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[Continued on next page]

### (54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

#### 11729.1 contg

#### 11729-45.21.21.cons1

#### 11729-45.21.21.cons2

#### 11731.lcontig

TETTITICTTICGATTICCTTCAATTIGTCACGTTTGATTTTATGAAGTTGTTCAAGGGCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCTTAGATGCAGTTCCTTAATGATAATC
CAACAGCATCTAATTGTTCTTTAAGTCTTTAGGCATAATTCTTCCTTTTCTGATGACTTTTTATGAGTAAACT
GATCCCTGAATCAGGTGTTACTGAGCTGCATGTTTTTATTCTTTTCGTTTAATAGCTCCTTCTCAGGGACCA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTTGTTGAAGTTGTTTGATTTCCATAATTTCCAGGTCACAC
TGTTTATCCAAAACTTCTAACTCAGTCTTTGTTGTTTGGTTTCGATTTCGAGACTCTGGACATGC
CTGCTTGATGTTTCCACTTCCAGTCCTCCAGTTCCAGGTGAGACTTTXCTTTCTGGAGCTCAGCCTGACAATGC
CTTCTTGTTGCTCCCTT

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used for the diagnosis and monitoring of ovarian cancer.

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# COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

### **Technical Field**

The present invention relates generally to ovarian cancer therapy. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian carcinoma protein, and to polynucleotides encoding such polypeptides, as well as antibodies and immune system cells that specifically recognize such polypeptides. Such polypeptides, polynucleotides, antibodies and cells may be used in vaccines and pharmaceutical compositions for treatment of ovarian cancer.

# 10 Background of the Invention

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Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor antigens and for using such antigens in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

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Briefly stated, this invention provides compositions and methods for the therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished. Within certain embodiments, the ovarian carcinoma protein comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:456-457, 460-477 and 512-570 and complements of such polynucleotides.

The present invention further provides polynucleotides that encode a polypeptide as described above or a portion thereof, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596.

Within other aspects, the present invention provides pharmaceutical compositions and vaccines. Pharmaceutical compositions may comprise a physiologically acceptable carrier or excipient in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma proteinspecific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. Vaccines may comprise a non-specific immune response enhancer in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions

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and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an anti-idiotypic antibody that is specifically bound by an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for 20 inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for stimulating and/or expanding T cells, comprising contacting T cells with (a) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (b) a polynucleotide encoding such a polypeptide and/or (c) an antigen presenting cell that

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expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Such polypeptide, polynucleotide and/or antigen presenting cell(s) may be present within a pharmaceutical composition or vaccine, for use in stimulating and/or expanding T cells in a mammal.

Within other aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared as described above.

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Within further aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (ii) a polynucleotide encoding such a polypeptide; or (iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of ovarian cancer in the patient. The proliferated cells may be cloned prior to administration to the patient.

The present invention also provides, within other aspects, methods for identifying secreted tumor antigens. Such methods comprise the steps of: (a) implanting tumor cells in an immunodeficient mammal; (b) obtaining serum from the immunodeficient mammal after a time sufficient to permit secretion of tumor antigens into the serum; (c) immunizing an immunocompetent mammal with the serum; (d) obtaining antiserum from the immunocompetent mammal; and (e) screening a tumor expression library with the antiserum, and therefrom identifying a secreted tumor antigen. A preferred method for identifying a secreted ovarian carcinoma antigen comprises the steps of: (a) implanting ovarian carcinoma cells in a SCID mouse; (b) obtaining serum from the SCID mouse after a time sufficient to permit secretion of

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ovarian carcinoma antigens into the serum; (c) immunizing an immunocompetent mouse with the serum; (d) obtaining antiserum from the immunocompetent mouse; and (e) screening an ovarian carcinoma expression library with the antiserum, and therefrom identifying a secreted ovarian carcinoma antigen.

The present invention also discloses antibody epitopes recognized by the O8E polyclonal anti-sera which epitopes are presented herein as SEQ ID NO: 394-415.

Further disclosed by the present invention are 10-mer and 9-mer peptides predicted to bind HLA-0201 which peptides are disclosed herein as SEQ ID NO:416-435 and SEQ ID NO:436-455, respectively.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

In another aspect of the present invention, the applicants have unexpectedly identified a series of novel repeating sequence elements in the 5' end of the gene encoding O772P. Therefore, the present invention provides O772P polypeptides having structures represented by  $X_n$ -Y, wherein X comprises a sequence having at least 50% identity, preferably at least 70% identity, and more preferably at least 90% identity with an O772P repeat sequence set forth in SEQ ID NO: 596. Y will typically comprise a sequence having at least 80% identity, preferably at least 90% identity and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 594. According to this embodiment, n will generally be an integer from 1 to 35, preferably an integer from 15 to 25, and X can be the same or different.

In one preferred embodiment, X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593 and Y comprises the sequence set forth in SEQ ID NO: 594.

In another preferred embodiment, an illustrative O772P polypeptide comprises the sequence set forth in SEQ ID NO: 595, containing 20 repeating sequence elements (i.e.,  $X_{20}$ ) wherein the X elements are arranged in the following order (moving from N-terminal to C-terminal in the O772P repeat region): SEQ ID NO: 574 - SEQ ID

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NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593.

According to another aspect of the present invention, an O772P polynucleotide is provided having the structure  $X_n$ -Y, wherein X comprises an O772P repeat sequence element selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567. Y will generally comprise a sequence having at least 80% identity, preferably at least 90% identity, and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568. In this embodiment, n is typically an integer from 1 to 35, preferably from 15 to 25 and X can be the same or different.

In another embodiment, an illustrative O772P polynucleotide comprises the sequence set forth in SEQ ID NO: 569, containing 20 repeating sequence elements (i.e., X<sub>20</sub>).

According to another aspect of the present invention, O772 polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.

According to another aspect of the present invention, O8E polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.

# BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS AND DRAWINGS

SEQ ID NO:1-71 are ovarian carcinoma antigen polynucleotides shown 25 in Figures 1A-1S.

SEQ ID NO:72-74 are ovarian carcinoma antigen polynucleotides shown in Figures 2A-2C.

SEQ ID NO:75 is the ovarian carcinoma polynucleotide 3g (Figure 4).

SEQ ID NO:76 is the ovarian carcinoma polynucleotide 3f (Figure 5).

SEQ ID NO:77 is the ovarian carcinoma polynucleotide 6b (Figure 6).

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SEQ ID NO:78 is the ovarian carcinoma polynucleotide 8e (Figure 7A).

SEQ ID NO:79 is the ovarian carcinoma polynucleotide 8h (Figure 7B).

SEQ ID NO:80 is the ovarian carcinoma polynucleotide 12e (Figure 8).

SEQ ID NO:81 is the ovarian carcinoma polynucleotide 12h (Figure 9).

SEQ ID NO:82-310 are ovarian carcinoma antigen polynucleotides shown in Figures 15A-15EEE.

SEQ ID NO:311 is a full length sequence of ovarian carcinoma polynucleotide O772P.

SEQ ID NO:312 is the O772P amino acid sequence.

SEQ ID NO:313-384 are ovarian carcinoma antigen polynucleotides.

SEQ ID NO:385 represents the cDNA sequence of a form of the clone O772P, designated 21013.

SEQ ID NO:386 represents the cDNA sequence of a form of the clone O772P, designated 21003.

SEQ ID NO:387 represents the cDNA sequence of a form of the clone O772P, designated 21008.

SEQ ID NOs:388 is the amino acid sequence corresponding to SEQ ID NO:385.

SEQ ID NOs:389 is the amino acid sequence corresponding to SEQ ID NO:386.SEQ ID NOs:390 is the amino acid sequence corresponding to SEQ ID NO:387.

SEQ ID NO:391 is a full length sequence of ovarian carcinoma polynucleotide O8E.

SEQ ID NO:392-393 are protein sequences encoded by O8E.

SEQ ID NO:394-415 are peptide sequences corresponding to the OE8 antibody epitopes.

SEQ ID NO:416-435 are potential HLA-A2 10-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:436-455 are potential HLA-A2 9-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:456 is a truncated nucleotide sequence of the full length Genbank sequence showing homology to O772P

SEQ ID NO:457 is the full length Genbank sequence showing significant homology to O772P

SEQ ID NO:458 is a protein encoding a truncated version of the full length Genbank sequence showing homology to O772P

SEQ ID NO:459 is the full length protein sequence from Genbank showing significant homology to the protein sequence for O772P

SEQ ID NO:460 encodes a unique N-terminal portion of O772P contained in residues 1-70.

SEQ ID NO:461 contains unique sequence and encodes residues 1-313 of SEQ ID NO: 456.

SEQ ID NO:462 is the hypothetical sequence for clone O772P.

SEQ ID NO:463 is the cDNA sequence for clone FLJ14303.

15 SEQ ID NO:464 is a partial cDNA sequence for clone O772P.

SEQ ID NO:465 is a partial cDNA sequence for clone O772P.

SEQ ID NO:466 is a partial cDNA sequence for clone O772P.

SEQ ID NO:467 is a partial cDNA sequence for clone O772P.

SEQ ID NO:468 is a partial cDNA sequence for clone O772P.

SEQ ID NO:469 is a partial cDNA sequence for clone O772P.

SEQ ID NO:470 is a partial cDNA sequence for clone O772P.

SEQ ID NO:471 is a partial cDNA sequence for clone O772P.

SEQ ID NO:472 is a partial cDNA sequence for clone O772P.

SEQ ID NO:473 is a partial cDNA sequence for clone O772P.

SEQ ID NO:474 is a partial cDNA sequence for clone O772P.

SEQ ID NO:475 is a partial cDNA sequence for clone O772P.

SEQ ID NO:476 is a partial cDNA sequence for clone O772P.

SEQ ID NO:477 represents the novel 5'-end of the ovarian tumor antigen

O772P.

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SEQ ID NO:478 is the amino acid sequence encoded by SEQ ID NO:462.

SEQ ID NO:479 is the amino acid sequence encoded by SEQ ID NO:463.

SEQ ID NO:480 is a partial amino acid sequence encoded by SEQ ID NO:472.

SEQ ID NO:481 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:471.

SEQ ID NO:482 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:471.

SEQ ID NO:483 is a partial amino acid sequence encoded by SEQ ID NO:467.

SEQ ID NO:484 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:466.

SEQ ID NO:485 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:466.

SEQ ID NO:486 is a partial amino acid sequence encoded by SEQ ID NO:465.

SEQ ID NO:487 is a partial amino acid sequence encoded by SEQ ID NO:464.

SEQ ID NO:488 represents the extracellular, transmembrane and 20 cytoplasmic regions of O772P.

SEQ ID NO:489 represents the predicted extracellular domain of O772P.

SEQ ID NO:490 represents the amino acid sequence of peptide #2 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:491 represents the amino acid sequence of peptide #6 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:492 represents the amino acid sequence of peptide #7 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:493 represents the amino acid sequence of peptide #8 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:494 represents the amino acid sequence of peptide #9 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:495 represents the amino acid sequence of peptide #11 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:496 represents the amino acid sequence of peptide #13 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:497 represents the amino acid sequence of peptide #22 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:498 represents the amino acid sequence of peptide #24 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:499 represents the amino acid sequence of peptide #27 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:500 represents the amino acid sequence of peptide #40 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:501 represents the amino acid sequence of peptide #41 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:502 represents the amino acid sequence of peptide #47 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:503 represents the amino acid sequence of peptide #50 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:504 represents the amino acid sequence of peptide #51 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:505 represents the amino acid sequence of peptide #52 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:506 represents the amino acid sequence of peptide #53 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:507 represents the amino acid sequence of peptide #58 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:508 represents the amino acid sequence of peptide #59 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:509 represents the amino acid sequence of peptide #60 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:510 represents the amino acid sequence of peptide #61 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:511 represents the amino acid sequence of peptide #71 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:512 (O772P repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:513 (O772P repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:514 (O772P repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:515 (O772P repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:516 (O772P repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:517 (HB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:518 (HB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:519 (HB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:520 (HB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:521 (HB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:522 (HB repeat6 5'-end) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:523 (1043400.1 repeat1) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:524 (1043400.1 repeat2) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

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SEQ ID NO:525 (1043400.1 repeat3) represents an example of a cDNA sequence corresponding to repeat number 10/11 from the 5' variable region of O772P.

SEQ ID NO:526 (1043400.1 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:527 (1043400.1 repeat5) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:528 (1043400.1 repeat6) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:529 (1043400.3 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:530 (1043400.3 repeat2) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:531 (1043400.5 repeat1) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:532 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P, in addition containing intron sequence.

SEQ ID NO:533 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:534 (1043400.8 repeat1) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:535 (1043400.8 repeat2) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:536 (1043400.8 repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:537 (1043400.9 repeat1) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:538 (1043400.9 repeat2) represents an example of a cDNA sequence corresponding to repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:539 (1043400.9 repeat3) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

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SEQ ID NO:540 (1043400.9 repeat4) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:541 (1043400.11 repeat1) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:542 (1043400.11 repeat2) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:543 (1043400.11 repeat3) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:544 (1043400.11 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:545 (1043400.11 repeat5) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:546 (1043400.12 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:547 (PB repeatA) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:548 (PB repeatB) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:549 (PB repeatE) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:550 (PB repeatG) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:551 (PB repeatC) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:552 (PB repeatH) represents an example of a cDNA sequence corresponding to repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:553 (PB repeat) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:554 (PB repeatK) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

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SEQ ID NO:555 (PB repeatD) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:556 (PB repeatl) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:557 (PB repeatM) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:558 (PB repeat9) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:559 (PB repeat8.5) represents an example of a cDNA sequence corresponding to repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:560 (PB repeat8) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:561 (PB repeat7) represents an example of a cDNA sequence corresponding to repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:562 (PB repeat6) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:563 (PB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:564 (PB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:565 (PB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:566 (PB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:567 (PB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:568 represents the cDNA sequence form the 3' constant region.

SEQ ID NO:569 represents a cDNA sequence containing the consensus sequences of the 21 repeats, the 3' constant region and the 3' untranslated region.

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SEQ ID NO:570 represents the cDNA sequence of the consensus repeat sequence.

SEQ ID NO:571 represents the consensus amino acid sequence of one potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:572 represents the consensus amino acid sequence of a second potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:573 represents the consensus amino acid sequence of a third potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:574 represents the consensus amino acid sequence of repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:575 represents the consensus amino acid sequence of repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:576 represents the consensus amino acid sequence of repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:577 represents the consensus amino acid sequence of repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:578 represents the consensus amino acid sequence of repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:579 represents the consensus amino acid sequence of repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:580 represents the consensus amino acid sequence of repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:581 represents the consensus amino acid sequence of repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:582 represents the consensus amino acid sequence of repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:583 represents the consensus amino acid sequence of repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:584 represents the consensus amino acid sequence of repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:585 represents the consensus amino acid sequence of repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:586 represents the consensus amino acid sequence of repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:587 represents the consensus amino acid sequence of repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:588 represents the consensus amino acid sequence of repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:589 represents the consensus amino acid sequence of repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:590 represents the consensus amino acid sequence of repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:591 represents the consensus amino acid sequence of repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:592 represents the consensus amino acid sequence of repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:593 represents the consensus amino acid sequence of repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:594 represents the amino acid sequence of the 3' constant 20 region.

SEQ ID NO:595 represents an amino acid sequence containing the consensus sequences of the 21 repeats and the 3' constant region.

SEQ ID NO:596 represents the amino acid sequence of the consensus repeat sequence.

Figures 1A-1S (SEQ ID NO:1-71) depict partial sequences of polynucleotides encoding representative secreted ovarian carcinoma antigens.

Figure 2A-2C depict full insert sequences for three of the clones of Figure 1. Figure 2A shows the sequence designated O7E (11731; SEQ ID NO:72), Figure 2B shows the sequence designated O9E (11785; SEQ ID NO:73) and Figure 2C shows the sequence designated O8E (13695; SEQ ID NO:74).

Figure 3 presents results of microarray expression analysis of the ovarian carcinoma sequence designated O8E.

Figure 4 presents a partial sequence of a polynucleotide (designated 3g; SEQ ID NO:75) encoding an ovarian carcinoma sequence that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX and osteonectin.

Figure 5 presents the ovarian carcinoma polynucleotide designated 3f (SEQ ID NO:76).

Figure 6 presents the ovarian carcinoma polynucleotide designated 6b (SEQ ID NO:77).

Figures 7A and 7B present the ovarian carcinoma polynucleotides designated 8e (SEQ ID NO:78) and 8h (SEQ ID NO:79).

Figure 8 presents the ovarian carcinoma polynucleotide designated 12c (SEQ ID NO:80).

Figure 9 presents the ovarian carcinoma polynucleotide designated 12h (SEQ ID NO:81).

Figure 10 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 3f.

Figure 11 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 6b.

Figure 12 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 8e.

Figure 13 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12c.

Figure 14 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12h.

Figures 15A-15EEE depict partial sequences of additional polynucleotides encoding representative secreted ovarian carcinoma antigens (SEQ ID NO:82-310).

Figure 16 is a diagram illustrating the location of various partial O8E sequences within the full length sequence.

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Figure 17 is a graph illustrating the results of epitope mapping studies on O8E protein.

Figure 18 is graph of a fluorescence activated cell sorting (FACS) analysis of O8E cell surface expression.

Figure 19 is graph of a FACS analysis of O8E cell surface expression.

Figure 20 shows FACS analysis results for O8E transfected HEK293 cells demonstrating cell surface expression of O8E.

Figure 21 shows FACS analysis results for SKBR3 breast tumor cells demonstrating cell surface expression of O8E.

Figure 22 shows 08E expression in HEK 293 cells. The cells were probed with anti-08E rabbit polyclonal antisera #2333L.

Figure 23 shows the ELISA analysis of anti-08E rabbit sera.

Figure 24 shows the ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody.

Figure 25 is a graph determining antibody internalization of anti-O8E mAb showing that mAbs against amino acids 61-80 induces ligand internalization.

#### DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy of cancer, such as ovarian cancer. The compositions described herein may include immunogenic polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies that bind to a polypeptide, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells).

Polypeptides of the present invention generally comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof. Certain ovarian carcinoma proteins have been identified using an immunoassay technique, and are referred to herein as ovarian carcinoma antigens. An "ovarian carcinoma antigen" is a protein that is expressed by ovarian tumor cells (preferably human cells) at a level that is at least two fold higher than the level in normal ovarian cells. Certain ovarian carcinoma antigens react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera generated against serum from an immunodeficient animal

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implanted with a human ovarian tumor. Such ovarian carcinoma antigens are shed or secreted from an ovarian tumor into the sera of the immunodeficient animal. Accordingly, certain ovarian carcinoma antigens provided herein are secreted antigens. Certain nucleic acid sequences of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence.

The present invention further provides ovarian carcinoma sequences that are identified using techniques to evaluate altered expression within an ovarian tumor. Such sequences may be polynucleotide or protein sequences. Ovarian carcinoma sequences are generally expressed in an ovarian tumor at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal ovarian tissue, as determined using a representative assay provided herein. Certain partial ovarian carcinoma polynucleotide sequences are presented herein. Proteins encoded by genes comprising such polynucleotide sequences (or complements thereof) are also considered ovarian carcinoma proteins.

Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to at least a portion of an ovarian carcinoma polypeptide as described herein. T cells that may be employed within the compositions provided herein are generally T cells (e.g., CD4<sup>+</sup> and/or CD8<sup>+</sup>) that are specific for such a polypeptide. Certain methods described herein further employ antigen-presenting cells (such as dendritic cells or macrophages) that express an ovarian carcinoma polypeptide as provided herein.

### Ovarian Carcinoma Polynucleotides

Any polynucleotide that encodes an ovarian carcinoma protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides, and more preferably at least 45 consecutive nucleotides, that encode a portion of an ovarian carcinoma protein. More preferably, a polynucleotide encodes an immunogenic portion of an ovarian carcinoma protein, such as an ovarian carcinoma antigen. Polynucleotides complementary to any

such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an ovarian carcinoma protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native ovarian carcinoma protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native ovarian carcinoma protein or a portion thereof.

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The percent identity for two polynucleotide or polypeptide sequences may be readily determined by comparing sequences using computer algorithms well known to those of ordinary skill in the art, such as Megalign, using default parameters. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Optimal alignment of sequences for comparison may be conducted, for example, using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. Preferably, the percentage of sequence identity is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the window may comprise additions or deletions (i.e., gaps) of 20 % or less, usually 5 to 15 %, or 10 to 12%, relative to the reference sequence (which does not contain additions or

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deletions). The percent identity may be calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e., the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native ovarian carcinoma protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, an ovarian carcinoma polynucleotide may be identified, as described in more detail below, by screening a late passage ovarian tumor expression library with antisera generated against sera of immunocompetent mice after injection of such mice with sera from SCID mice implanted with late passage ovarian tumors. Ovarian carcinoma polynucleotides may also be identified using any of a variety of techniques designed to evaluate differential gene expression. Alternatively, polynucleotides may

be amplified from cDNA prepared from ovarian tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., an ovarian carcinoma cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target

sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl.

Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

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Certain nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma antigens are provided in Figures 1A-1S (SEQ ID NO:1 to 71) and Figures 15A to 15EEE (SEQ ID NO:82 to 310). The sequences provided in Figures 1A-1S appear to be novel. For sequences in Figures 15A-15EEE, database searches revealed matches having substantial identity. These polynucleotides were isolated by serological screening of an ovarian tumor cDNA expression library, using a technique designed to identify secreted tumor antigens. Briefly, a late passage ovarian tumor expression library was prepared from a SCID-derived human ovarian tumor (OV9334) in the vector λ-screen (Novagen). The sera used for screening were obtained by

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injecting immunocompetent mice with sera from SCID mice implanted with one late passage ovarian tumors. This technique permits the identification of cDNA molecules that encode immunogenic portions of secreted tumor antigens.

The polynucleotides recited herein, as well as full length polynucleotides comprising such sequences, other portions of such full length polynucleotides, and sequences complementary to all or a portion of such full length molecules, are specifically encompassed by the present invention. It will be apparent to those of ordinary skill in the art that this technique can also be applied to the identification of antigens that are secreted from other types of tumors.

Other nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma proteins are provided in Figures 4-9 (SEQ ID NO:75-81), as well as SEQ ID NO:313-384. These sequences were identified by screening a microarray of cDNAs for tumor-associated expression (i.e., expression that is at least five fold greater in an ovarian tumor than in normal ovarian tissue, as determined using a representative assay provided herein). Such screens were performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). SEQ ID NO:311 and 391 provide full length sequences incorporating certain of these nucleic acid sequences.

Any of a variety of well known techniques may be used to evaluate tumor-associated expression of a cDNA. For example, hybridization techniques using labeled polynucleotide probes may be employed. Alternatively, or in addition, amplification techniques such as real-time PCR may be used (see Gibson et al., Genome Research 6:995-1001, 1996; Heid et al., Genome Research 6:986-994, 1996). Real-time PCR is a technique that evaluates the level of PCR product accumulation during amplification. This technique permits quantitative evaluation of mRNA levels in multiple samples. Briefly, mRNA is extracted from tumor and normal tissue and cDNA is prepared using standard techniques. Real-time PCR may be performed, for example, using a Perkin Elmer/Applied Biosystems (Foster City, CA) 7700 Prism instrument. Matching primers and fluorescent probes may be designed for genes of interest using, for example, the primer express program provided by Perkin Elmer/Applied Biosystems

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(Foster City, CA). Optimal concentrations of primers and probes may be initially determined by those of ordinary skill in the art, and control (e.g.,  $\beta$ -actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, CA). To quantitate the amount of specific RNA in a sample, a standard curve is generated alongside using a plasmid containing the gene of interest. Standard curves may be generated using the Ct values determined in the real-time PCR, which are related to the initial cDNA concentration used in the assay. Standard dilutions ranging from  $10-10^6$  copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial RNA content of a tissue sample to the amount of control for comparison purposes.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding an ovarian carcinoma antigen, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo.

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells or tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of an ovarian carcinoma protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches,

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Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

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Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also

be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

### Ovarian Carcinoma Polypeptides

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Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof, as described herein. As noted above, certain ovarian carcinoma proteins are ovarian carcinoma antigens that are expressed by ovarian tumor cells and react detectably within an immunoassay (such as an ELISA) with antisera generated against serum from an immunodeficient animal implanted with an ovarian tumor. Other ovarian carcinoma proteins are encoded by ovarian carcinoma polynucleotides recited herein. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of an antigen that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an ovarian carcinoma protein or a variant thereof. Preferred immunogenic portions are encoded by cDNA molecules isolated as described herein. Further immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with ovarian carcinoma protein-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "ovarian carcinoma protein-

specific" if they specifically bind to an ovarian carcinoma protein (i.e., they react with the ovarian carcinoma protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera, antibodies and T cells may be prepared as described herein, and using well known techniques. An immunogenic portion of a native ovarian carcinoma protein is a portion that reacts with such antisera, antibodies and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length protein. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

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As noted above, a composition may comprise a variant of a native ovarian carcinoma protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian carcinoma protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with ovarian carcinoma protein-specific antisera may be enhanced or unchanged, relative to the native ovarian carcinoma protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native ovarian carcinoma protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with ovarian carcinoma protein-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the native polypeptide. Preferably, a variant contains conservative substitutions. "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

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Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells

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include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises one polypeptide as described herein and a known tumor antigen, such as an ovarian carcinoma protein or a variant of such a protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, 30 including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused WO 02/06317 PCT/US01/22635

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protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

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Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen present cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

# **Binding Agents**

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to an ovarian carcinoma protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian carcinoma protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian carcinoma protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a "complex" is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant maybe determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a ovarian carcinoma antigen will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological

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samples (e.g., blood, sera, leukophoresis, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

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Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the

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desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include

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methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of

derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

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Also provided herein are anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein. Such antibodies may be raised against an antibody, or antigen-binding fragment thereof, that specifically binds to an

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immunogenic portion of an ovarian carcinoma protein, using well known techniques. Anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein are those antibodies that bind to an antibody, or antigen-binding fragment thereof, that specifically binds to an immunogenic portion of an ovarian carcinoma protein, as described herein.

### T Cells

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Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for an ovarian carcinoma protein. Such cells may generally be prepared in vitro or ex vivo, using standard procedures. For example, T cells may be present within 10 (or isolated from) bone marrow, peripheral blood or a fraction of bone marrow or peripheral blood of a mammal, such as a patient, using a commercially available cell separation system, such as the CEPRATETM system, available from CellPro Inc., Bothell WA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human animals, cell lines or cultures.

T cells may be stimulated with an ovarian carcinoma polypeptide, polynucleotide encoding an ovarian carcinoma polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, an ovarian carcinoma polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for an ovarian carcinoma polypeptide if the T cells kill target cells coated with an ovarian carcinoma polypeptide or expressing a gene encoding such a polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be

accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with an ovarian carcinoma polypeptide (200 ng/ml - 100 µg/ml, preferably 100 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells and/or contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998). T cells that have been activated in response to an ovarian carcinoma polypeptide, polynucleotide or ovarian carcinoma polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Ovarian carcinoma polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient or a related or unrelated donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to an ovarian carcinoma polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to an ovarian carcinoma polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize an ovarian carcinoma polypeptide. Alternatively, one or more T cells that proliferate in the presence of an ovarian carcinoma polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution. Following expansion, the cells may be administered back to the patient as described, for example, by Chang et al., *Crit. Rev. Oncol. Hematol. 22*:213, 1996.

# Pharmaceutical Compositions and Vaccines

Within certain aspects, polypeptides, polynucleotides, binding agents 30 and/or immune system cells as described herein may be incorporated into

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pharmaceutical compositions or vaccines. Pharmaceutical compositions comprise one or more such compounds or cells and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds or cells and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., PNAS 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., PNAS 91:215-219, 1994; Kass-Eisler et al.,

PNAS 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer.

For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune

responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ), alum, biodegradable microspheres, monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). Also preferred is AS-2 (SmithKline Beecham). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO

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96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to

be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated ex vivo by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFa to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFa, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

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Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a ovarian carcinoma antigen (or portion or other variant thereof) such that the antigen, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

## Cancer Therapy

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as ovarian cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Within certain preferred embodiments, a patient is afflicted with ovarian cancer. Such cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immuno response-modifying agents (such as tumor vaccines, bacterial adjuvants and/or cytokines).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigenpresenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system.

Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., 5 Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into stem cells taken from a patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration), orally or in the bed of a resected tumor. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level.. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical

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outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to an ovarian carcinoma antigen generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

## Screens for Identifying Secreted Ovarian Carcinoma Antigens

The present invention provides methods for identifying secreted tumor antigens. Within such methods, tumors are implanted into immunodeficient animals such as SCID mice and maintained for a time sufficient to permit secretion of tumor antigens into serum. In general, tumors may be implanted subcutaneously or within the gonadal fat pad of an immunodeficient animal and maintained for 1-9 months, preferably 1-4 months. Implantation may generally be performed as described in WO 97/18300. The serum containing secreted antigens is then used to prepare antisera in immunocompetent mice, using standard techniques and as described herein. Briefly, 50-100 µL of sera (pooled from three sets of immunodeficient mice, each set bearing a different SCID-derived human ovarian tumor) may be mixed 1:1 (vol:vol) with an appropriate adjuvant, such as RIBI-MPL or MPL + TDM (Sigma Chemical Co., St. Louis, MO) and injected intraperitoneally into syngeneic immunocompetent animals at monthly intervals for a total of 5 months. Antisera from animals immunized in such a manner may be obtained by drawing blood after the third, fourth and fifth immunizations. The resulting antiserum is generally pre-cleared of E. coli and phage antigens and used (generally following dilution, such as 1:200) in a serological expression screen.

The library is typically an expression library containing cDNAs from one or more tumors of the type that was implanted into SCID mice. This expression library may be prepared in any suitable vector, such as  $\lambda$ -screen (Novagen). cDNAs that encode a polypeptide that reacts with the antiserum may be identified using standard techniques, and sequenced. Such cDNA molecules may be further characterized to

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evaluate expression in tumor and normal tissue, and to evaluate antigen secretion in patients.

The methods provided herein have advantages over other methods for tumor antigen discovery. In particular, all antigens identified by such methods should be secreted or released through necrosis of the tumor cells. Such antigens may be present on the surface of tumor cells for an amount of time sufficient to permit targeting and killing by the immune system, following vaccination.

# Methods for Detecting Cancer

In general, a cancer may be detected in a patient based on the presence of one or more ovarian carcinoma proteins and/or polynucleotides encoding such proteins in a biological sample (such as blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of protein that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, an ovarian carcinoma-associated sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding

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agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian carcinoma proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

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Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over

a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups 15 and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as ovarian cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, 30 p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity)

that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

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In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

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Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use ovarian carcinoma polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian carcinoma protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with an ovarian carcinoma protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with an ovarian carcinoma protein, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with an ovarian carcinoma protein (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian carcinoma protein to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian carcinoma protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of an ovarian carcinoma protein cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the ovarian carcinoma protein. The amplified cDNA is then separated and detected using techniques well

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known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding an ovarian carcinoma protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding an ovarian carcinoma protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous 15 nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence provided herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample such as a biopsy tissue and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, ovarian carcinoma proteins and polynucleotides encoding such proteins may be used as markers for monitoring the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple ovarian carcinoma protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

# **Diagnostic Kits**

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The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to an ovarian carcinoma protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain

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a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian carcinoma protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding an ovarian carcinoma protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding an ovarian carcinoma protein.

The following Examples are offered by way of illustration and not by way of limitation.

## **EXAMPLES**

## **EXAMPLE 1**

# IDENTIFICATION OF REPRESENTATIVE OVARIAN CARCINOMA PROTEIN CDNAS

This Example illustrates the identification of cDNA molecules encoding ovarian carcinoma proteins.

Anti-SCID mouse sera (generated against sera from SCID mice carrying late passage ovarian carcinoma) was pre-cleared of E. coli and phage antigens and used at a 1:200 dilution in a serological expression screen. The library screened was made from a SCID-derived human ovarian tumor (OV9334) using a directional RH oligo(dT) priming cDNA library construction kit and the λScreen vector (Novagen). A bacteriophage lambda screen was employed. Approximately 400,000 pfu of the amplified OV9334 library were screened.

196 positive clones were isolated. Certain sequences that appear to be novel are provided in Figures 1A-1S and SEQ ID NO:1 to 71. Three complete insert sequences are shown in Figures 2A-2C (SEQ ID NO:72 to 74). Other clones having known sequences are presented in Figures 15A-15EEE (SEQ ID NO:82 to 310). Database searches identified the following sequences that were substantially identical to the sequences presented in Figures 15A-15EEE.

These clones were further characterized using microarray technology to

determine mRNA expression levels in a variety of tumor and normal tissues. Such
analyses were performed using a Synteni (Palo Alto, CA) microarray, according to the
manufacturer's instructions. PCR amplification products were arrayed on slides, with
each product occupying a unique location in the array. mRNA was extracted from the
tissue sample to be tested, reverse transcribed and fluorescent-labeled cDNA probes
were generated. The microarrays were probed with the labeled cDNA probes and the
slides were scanned to measure fluorescence intensity. Data was analyzed using
Synteni's provided GEMtools software. The results for one clone (13695, also referred
to as O8E) are shown in Figure 3.

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#### **EXAMPLE 2**

## IDENTIFICATION OF OVARIAN CARCINOMA CDNAs USING MICROARRAY TECHNOLOGY

This Example illustrates the identification of ovarian carcinoma polynucleotides by PCR subtraction and microarray analysis. Microarrays of cDNAs 5 were analyzed for ovarian tumor-specific expression using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., Proc. Natl. Acad. Sci. USA 93:10614-10619, 1996 and Heller et al., Proc. Natl. Acad. Sci. USA 94:2150-2155, 1997).

A PCR subtraction was performed using a tester comprising cDNA of four ovarian tumors (three of which were metastatic tumors) and a driver of cDNA form 10 five normal tissues (adrenal gland, lung, pancreas, spleen and brain). cDNA fragments recovered from this subtraction were subjected to DNA microarray analysis where the fragments were PCR amplified, adhered to chips and hybridized with fluorescently labeled probes derived from mRNAs of human ovarian tumors and a variety of normal human tissues. In this analysis, the slides were scanned and the fluorescence intensity was measured, and the data were analyzed using Synteni's GEMtools software. In general, sequences showing at least a 5-fold increase in expression in tumor cells (relative to normal cells) were considered ovarian tumor antigens. The fluorescent results were analyzed and clones that displayed increased expression in ovarian tumors were further characterized by DNA sequencing and database searches to determine the novelty of the sequences.

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Using such assays, an ovarian tumor antigen was identified that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX (see Jin et al., Cell 93:81-91, 1998) and an extracellular matrix protein called osteonectin. A splice junction sequence exists at the fusion point. The sequence of this clone is presented in Figure 4 and SEQ ID NO:75. Osteonectin, unspliced and unaltered, was also identified from such assays independently.

Further clones identified by this method are referred to herein as 3f, 6b, 8e, 8h, 12c and 12h. Sequences of these clones are shown in Figures 5 to 9 and SEO ID NO:76 to 81. Microarray analyses were performed as described above, and are presented in Figures 10 to 14. A full length sequence encompassing clones 3f, 6b, 8e and 12h was obtained by screening an ovarian tumor (SCID-derived) cDNA library. This 2996 base pair sequence (designated O772P) is presented in SEQ ID NO:311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO:312. PSORT analysis indicates a Type 1a transmembrane protein localized to the plasma membrane.

In addition to certain of the sequences described above, this screen identified the following sequences which are described in detail in Table 1:

Table 1

Sequence	Comments
OV4vG11 (SEQ ID NO:313)	human clone 1119D9 on chromosome 20p12
OV4vB11 (SEQ ID NO:314)	human UWGC:y14c094 from chromosome 6p21
OV4vD9 (SEQ ID NO:315)	human clone 1049G16 chromosome 20q12-13.2
OV4vD5 (SEQ ID NO:316)	human KIAA0014 gene
OV4vC2 (SEQ ID NO:317)	human KIAA0084 gene
OV4vF3 (SEQ ID NO:318)	human chromosome 19 cosmid R31167
OV4VC1 (SEQ ID NO:319)	novel
OV4vH3 (SEQ ID NO:320)	novel
OV4vD2 (SEQ ID NO:321)	novel
O815P (SEQ ID NO:322)	novel
OV4vC12 (SEQ ID NO:323)	novel
OV4vA4 (SEQ ID NO:324)	novel
OV4vA3 (SEQ ID NO:325)	novel
OV4v2A5 (SEQ ID NO:326)	novel
O819P (SEQ ID NO:327)	novel
O818P (SEQ ID NO:328)	novel
O817P (SEQ ID NO:329)	novel
O816P (SEQ ID NO:330)	novel
Ov4vC5 (SEQ ID NO:331)	novel
21721 (SEQ ID NO:332)	human lumican
21719 (SEQ ID NO:333)	human retinoic acid-binding protein II
21717 (SEQ ID NO:334)	human26S proteasome ATPase subunit
21654 (SEQ ID NO:335)	human copine I
21627 (SEQ ID NO:336)	human neuron specific gamma-2 enolase

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Sequence	Comments		
21623 (SEQ ID NO:337)	human geranylgeranyl transferase II		
21621 (SEQ ID NO:338)	human cyclin-dependent protein kinase		
21616 (SEQ ID NO:339)	human prepro-megakaryocyte potentiating factor		
21612 (SEQ ID NO:340)	human UPH1		
21558 (SEQ ID NO:341)	human RalGDS-like 2 (RGL2)		
21555 (SEQ ID NO:342)	human autoantigen P542		
21548 (SEQ ID NO:343)	human actin-related protein (ARP2)		
21462 (SEQ ID NO:344)	human huntingtin interacting protein		
21441 (SEQ ID NO:345)	human 90K product (tumor associated antigen)		
21439 (SEQ ID NO:346)	human guanine nucleotide regulator protein (tim1)		
21438 (SEQ ID NO:347)	human Ku autoimmune (p70/p80) antigen		
21237 (SEQ ID NO:348)	human S-laminin		
21436 (SEQ ID NO:349)	human ribophorin I		
21435 (SEQ ID NO:350)	human cytoplasmic chaperonin hTRiC5		
21425 (SEQ ID NO:351)	humanEMX2		
21423 (SEQ ID NO:352)	human p87/p89 gene		
21419 (SEQ ID NO:353)	human HPBRII-7		
21252 (SEQ ID NO:354)	human T1-227H		
21251 (SEQ ID NO:355)	human cullin I		
21247 (SEQ ID NO:356)	kunitz type protease inhibitor (KOP)		
21244-1 (SEQ ID NO:357)	human protein tyrosine phosphatase receptor F (PTPRF)		
21718 (SEQ ID NO:358)	human LTR repeat		
OV2-90 (SEQ ID NO:359)	novel		
Human zinc finger (SEQ ID NO:	Human zinc finger (SEQ ID NO:360)		
Human polyA binding protein (SEQ ID NO:361)			
Human pleitrophin (SEQ ID NO:362)			
Human PAC clone 278C19 (SEQ ID NO:363)			
Human LLRep3 (SEQ ID NO:364)			
Human Kunitz type protease inhib (SEQ ID NO:365)			
Human KIAA0106 gene (SEQ ID NO:366)			
Human keratin (SEQ ID NO:367)			
Human HIV-1TAR (SEQ ID NO:368)			
Human glia derived nexin (SEQ ID NO:369)			

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Sequence	Comments	
Human fibronectin (SEQ ID NO:370)		
Human ECMproBM40 (SEQ ID NO:371)		
Human collagen (SEQ ID NO:372)		
Human alpha enolase (SEQ ID NO:373)		
Human aldolase (SEQ ID NO:374)		
Human transf growth factor BIG H3 (SEQ ID NO:375)		
Human SPARC osteonectin (SEQ ID NO:376)		
Human SLP1 leucocyte protease (SEQ ID NO:377)		
Human mitochondrial ATP synth (SEQ ID NO:378)		
Human DNA seq clone 461P17 (SEQ ID NO:379)		
Human dbpB pro Y box (SEQ ID NO:380)		
Human 40 kDa keratin (SEQ ID NO:381)		
Human arginosuccinate synth (SEQ ID NO:382)		
Human acidic ribosomal phosphoprotein (SEQ ID NO:383)		
Human colon carcinoma laminin binding pro (SEQ ID NO:384)		

This screen further identified multiple forms of the clone O772P, referred to herein as 21013, 21003 and 21008. PSORT analysis indicates that 21003 (SEQ ID NO:386; translated as SEQ ID NO:389) and 21008 (SEQ ID NO:387; translated as SEQ ID NO:390) represent Type 1a transmembrane protein forms of O772P. 21013 (SEQ ID NO:385; translated as SEQ ID NO:388) appears to be a truncated form of the protein and is predicted by PSORT analysis to be a secreted protein.

Additional sequence analysis resulted in a full length clone for O8E (2627 bp, which agrees with the message size observed by Northern analysis; SEQ ID NO:391). This nucleotide sequence was obtained as follows: the original O8E sequence (OrigO8Econs) was found to overlap by 33 nucleotides with a sequence from an EST clone (IMAGE#1987589). This clone provided 1042 additional nucleotides upstream of the original O8E sequence. The link between the EST and O8E was confirmed by sequencing multiple PCR fragments generated from an ovary primary tumor library using primers to the unique EST and the O8E sequence (ESTxO8EPCR). Full length status was further indicated when anchored PCR from the ovary tumor library gave

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several clones (AnchoredPCR cons) that all terminated upstream of the putative start methionine, but failed to yield any additional sequence information. Figure 16 presents a diagram that illustrates the location of each partial sequence within the full length O8E sequence.

Two protein sequences may be translated from the full length O8E. For "a" (SEQ ID NO:393) begins with a putative start methionine. A second form "b" (SEQ ID NO:392) includes 27 additional upstream residues to the 5' end of the nucleotide sequence.

#### **EXAMPLE 3**

This example discloses the identification and characterization of antibody epitopes recognized by the O8E polyclonal anti-sera.

Rabbit anti-sera was raised against E. coli derived O8E recombinant protein and tested for antibody epitope recognition against 20 or 21 mer peptides that correspond to the O8E amino acid sequence. Peptides spanning amino acid regions 31 to 65, 76 to 110, 136 to 200 and 226 to 245 of the full length O8E protein were recognized by an acid eluted peak and/or a salt eluted peak from affinity purified anti-O8E sera. Thus, the corresponding amino acid sequences of the above peptides constitute the antibody epitopes recognized by affinity purified anti-O8E antibodies.

ELISA analysis of anti-08E rabbit sera is shown in Figure 23, and ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody is shown in Figure 24.

For epitope mapping, 20 or 21 mer peptides corresponding to the O8E protein were synthesized. For antibody affinity purification, rabbit anti-O8E sera was run over an O8E-sepharose column, then antibody was eluted with a salt buffer containing 0.5 M NaCl and 20 mM PO<sub>4</sub>, followed by an acid elution step using 0.2 M Glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8 and buffer exchanged into phosphate buffered saline (PBS). For enzyme linked immunosorbant assay (ELISA) analysis, O8E peptides and O8E recombinant protein were coated onto 96 well flat bottom plates at 2 μg/ml for 2 hours at room temperature (RT). Plates were then washed 5 times with PBS + 0.1 % Tween 20 and blocked with PBS + 1 % bovine serum albumin (BSA) for 1 hour. Affinity purified anti-O8E antibody, either an acid or salt eluted fraction, was then added to the wells at 1 μg/ml

and incubated at RT for 1 hr. Plates were again washed, followed by the addition of donkey anti-rabbit-Ig-horseradish peroxidase (HRP) antibody for 1 hour at RT. Plates were washed, then developed by the addition of the chromagenic substrate 3, 3', 5, 5'-tetramethylbenzidine (TMB) (described by Bos et al., J. of Immunoassay 2:187-204 (1981); available from Sigma (St. Louis, MO)). The reaction was incubated 15 minutes at RT and then stopped by the addition of 1 N H<sub>2</sub>SO<sub>4</sub>. Plates were read at an optical density of 450 (OD450) in an automated plate reader. The sequences of peptides corresponding to the OE8 antibody epitopes are disclosed herein as SEQ ID NO: 394-415. Antibody epitopes recognized by the O8E polyclonal anti-sera are disclosed herein in Figure 17.

## **EXAMPLE 4**

This example discloses IHC analysis of O8E expression in ovarian cancer tissue samples.

For immunohistochemistry studies, paraffin-embedded formalin fixed ovarian cancer tissue was sliced into 8 micron sections. Steam heat induced epitope retrieval (SHIER) in 0.1 M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody (anti-O8E rabbit affinity purified polyclonal antibody) was added to each section for 25 min followed by a 25 min incubation with an anti-rabbit biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 min incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase system was used along with DAB chromogen to visualize antigen expression. Slides were counterstained with hematoxylin. One (papillary serous carcinoma) of six ovarian cancer tissue sections displayed O8E immunoreactivity. Upon optimization of the staining conditions, 4/5 ovarian cancer samples stained positive using the O8E polyclonal antibody. O8E expression was localized to the plasma membrane.

Six ovarian cancer tissues were analyzed with the anti-O8E rabbit polyclonal antibody. One (papillary serous carcinoma) of six ovarian cancer tissue samples stained positive for O8E expression. O8E expression was localized to the surface membrane.

#### EXAMPLE 5

This example discloses O8E peptides that are predicted to bind HLA-A2 and to be immunogenic for CD8 T cell responses in humans.

Potential HLA-A2 binding peptides of O8E were predicted by using the full-length open-reading frame (ORF) from O8E and running it through "Episeek," a program used to predict MHC binding peptides. The program used is based on the algorithm published by Parker, K.C. et al., J. Immunol. 152(1):163-175 (1994) (incorporated by reference herein in its entirety). 10-mer and 9-mer peptides predicted to bind HLA-0201 are disclosed herein as SEQ ID NO: 416-435 and SEQ ID NO: 436-10 455, respectively.

## **EXAMPLE 6**

This example discloses O8E cell surface expression measured by fluoresence activated cell sorting.

For FACS analysis, cells were washed with ice cold staining buffer (PBS/1% BSA/azide). Next, the cells were incubated for 30 minutes on ice with 10 micrograms/ml of affinity purified rabbit anti-B305D polyclonal antibody. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig (H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing prodium iodide, a vital stain that allows for identification of permeable cells, and analyzed by FACS. O8E surface expression was confirmed on SKBR3 breast cancer cells and HEK293 cells that stably overexpress the cDNA for O8E. Neither MB415 cells nor HEK293 cells stably transfected with a control irrelevant plasmid DNA showed surface expression of O8E (Figures 18 and 19).

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#### **EXAMPLE 7**

This example further evaluates the expression and surface localization of O8E.

For expression and purification of antigen used for immunization, O8E expressed in an E. coli recombinant expression system was grown overnight in LB Broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning,

10 ml of the overnight culture was added to 500 ml of 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nanometers) of the culture reached 0.4-0.6 the cells were induced with IPTG (1 mM). 4 hours after induction with IPTG the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty milliliters of lysis buffer was added to the cell pellets and vortexed. To break open the E. coli cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For protein that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0 , 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin such as Hi-Prep Q (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off of the column with an increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. This material was then evaluated for acceptable purity as determined by SDS-PAGE or HPLC, concentration as determined by Lowry assay or Amino Acid Analysis, identity as determined by amino terminal protein sequence, and endotoxin level as determined by the Limulus (LAL) assay. The

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proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

For generation of polyclonal anti-sera, 400 micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed. Every four weeks animals were boosted with 100 micrograms of antigen mixed with an equal volume of IFA. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

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For characterization of polyclonal antisera, 96 well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at RT for 2 hrs. Plates were washed 6 times with PBS/0.01% tween. Anti-O8E rabbit sera or affinity purified anti-O8e antibody was diluted in PBS. Fifty microliters of diluted antibody was added to each well and incubated at RT for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at RT for 30 min. Plates were washed as described above and 100 microliters of TMB microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature the colorimetric reaction was stopped with 100 microliters of 1N H2SO4 and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the O8E antigen.

For recombinant expression in mammalian HEK293 cells, full length O8E cDNA was subcloned into the mammalian expression vectors pcDNA3.1+ and pCEP4 (Invitrogen) which were modified to contain His and FLAG epitope tags, respectively. These constructs were transfected into HEK293 cells (ATCC) using Fugene 6 reagent (Roche). Briefly, HEK293 cells were plated at a density of 100,000 cells/ml in DMEM (Gibco) containing 10% FBS (Hyclone) and grown overnight. The following day, 2 ul of Fugene6 was added to 100 ul of DMEM containing no FBS and incubated for 15 minutes at room temperature. The Fugene6/DMEM mixture was then added to 1ug of O8E/pCEP4 or O8E/pcDNA3.1 plasmid DNA and incubated for 15 minutes at room temperature. The Fugene/DNA mix was then added to the HEK293

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cells and incubated for 48-72 hrs at 37oC with 7% CO2. Cells were rinsed with PBS then collected and pelleted by centrifugation. For Western blot analysis, whole cell lysates were generated by incubating the cells in Triton-X100 containing lysis buffer for 30 minutes on ice. Lysates were then cleared by centrifugation at 10,000rpm for 5 minutes at 4 C. Samples were diluted with SDS-PAGE loading buffer containing beta-mercaptoethanol, then boiled for 10 minutes prior to loading the SDS-PAGE gel. Protein was transferred to nitrocellulose and probed using anti-O8E rabbit polyclonal sera #2333L at a dilution of 1:750. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate.

For FACS analysis, cells were washed further with ice cold staining buffer (PBS+1%BSA+Azide). Next, the cells were incubated for 30 minutes on ice with 10ug/ml of Protein A purified anti-O8E polyclonal sera. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig(H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that allows for the identification of permeable cells, and analyzed by FACS.

From these experiments, the results of which are illustrated in Figures 20-21, O8E expression was detected on the surface of transfected HEK293 cells and SKBR3 cells by FACS analysis using rabbit anti-O8E sera. Expression was also detected in transfected HEK293 cell lysates by Western blot analysis (Figure 22).

#### **EXAMPLE 8**

# GENERATION AND CHARACTERIZATION OF ANTI-O8E MABS.

Mouse monoclonal antibodies were raised against E. coli derived O8E proteins as follows. A/J mice were immunized intraperitoneally (IP) with Complete Freund's Adjuvant (CFA) containing 50 µg recombinant O8E, followed by a subsequent IP boost with Incomplete Freund's Adjuvant (IFA) containing 10µg recombinant O8E protein. Three days prior to removal of the spleens, the mice were immunized intravenously with approximately 50µg of soluble O8E recombinant protein. The spleen of a mouse with a positive titer to O8E was removed, and a single-cell suspension made and used for fusion to SP2/0 myeloma cells to generate B cell

hybridomas. The supernatants from the hybrid clones were tested by ELISA for specificity to recombinant O8E, and epitope mapped using peptides that spanned the entire O8E sequence. The mAbs were also tested by flow cytometry for their ability to detect O8E on the surface of cells stably transfected with O8E and on the surface of a breast tumor cell line.

For ELISA analysis, 96 well plates were coated with either recombinant O8E protein or overlapping 20-mer peptides spanning the entire O8E molecule at a concentration of either 1-2µg/ml or 10µg/ml, respectively. After coating, the plates were washed 5 times with washing buffer (PBS + 0.1% Tween-20) and blocked with PBS containing 0.5% BSA, 0.4% Tween-20. Hybrid supernatants or purified mAbs were then added and the plates incubated for 60 minutes at room temperature. The plates were washed 5 times with washing buffer and the secondary antibody, donkey-anti mouse Ig linked to horseradish peroxidase (HRP)(Jackson ImmunoResearch), was added for 60 minutes. The plates were again washed 5 times in washing buffer, followed by the addition of the peroxidase substrate. Of the hybridoma clones generated, 15 secreted mAbs that recognized the entire O8E protein. Epitope mapping revealed that of these 15 clones, 14 secreted mAbs that recognized the O8E amino acid residues 61-80 and one clone secreted a mAb that recognized amino acid residues 151-170.

For flow cytometric analysis, HEK293 cells which had been stably transfected with O8E and SKBR3 cells which express O8E mRNA, were harvested and washed in flow staining buffer (PBS+1%BSA+Azide). The cells were incubated with the supernatant from the mAb hybrids for 30 minutes on ice followed by 3 washes with staining buffer. The cells were incubated with goat-anti mouse Ig-FTTC for 30 minutes on ice, followed by three washes with staining buffer before being resuspended in wash buffer containing propidium iodide. Flow cytometric analysis revealed that 15/15 mAbs were able to detect O8E protein expressed on the surface of O8E-transfected HEK293 cells. 6/6 mAbs tested on SKBR3 cells were able to recognize surface expressed O8E.

#### **EXAMPLE 9**

#### EXTENDED DNA AND PROTEIN SEQUENCE ANALYSIS OF SEQUENCE O772P

A full-length sequence encompassing clones 3f, 6b, 8e, and 12 was obtained by screening an ovarian tumor (SCID-derived) cDNA library described in detail in Example 2. This 2996 base pair sequence, designated O772P, is presented in SEQ ID NO: 311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO: 312. The DNA sequence O772P was searched against public databases including Genbank and showed a significant hit to Genbank Accession number AK024365 (SEQ ID NO: 457). This Genbank sequence was found to be 3557 base pairs in length and encodes a protein 1156 amino acids in length (SEO ID NO: 459). A truncated version of this sequence, residues 25-3471, in which residue 25 corresponds to the first ATG initiation codon in the Genbank sequence, (SEQ ID NO: 456), encodes a protein that is 1148 amino acids in length (SEQ ID NO: 458). The published DNA sequence (SEQ ID NO: 457) differs from O772P in that it has a 5 base pair insertion corresponding to bases 958-962 of SEQ ID NO: 457. This insertion results in a frame shift such that SEQ ID NO: 457 encodes an additional N-terminal protein sequence relative to O772P (SEQ ID NO: 312). In addition, O772P encodes a unique N-terminal portion contained in residues 1-79 (SEQ ID NO: 460). The N-terminal portion of SEQ ID NO: 456, residues 1-313, also contains unique sequence and is listed as SEQ ID NO: 461.

#### **EXAMPLE 10**

# THE GENERATION OF POLYCLONAL ANTIBODIES FOR IMMUNOHISTOCHEMISTRY AND FLOW CYTOMETRIC ANALYSIS OF THE CELL ASSOCIATED EXPRESSION PATTERN OF MOLECULE O772P

The O772P molecule was identified in Examples 2 and 9 of this application. To evaluate the subcellular localization and specificity of antigen expression in various tissues, polyclonal antibodies were generated against O772P. To produce these antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312) were expressed in an E. coli recombinant expression system and grown overnight at 37°C in LB Broth. The following day, 10ml

of the overnight culture was added to 500ml of 2xYT containing the appropriate antibiotics. When the optical density of the cultures (560 nanometers) reached 0.4-0.6 the cells were induced with IPTG. Following induction, the cells were harvested, washed, lysed and run through a French Press at a pressure of 16000 psi. The cells were then centrifuged and the pellet checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localize to the cell pellet, the pellet was resuspended in 10mM Tris, pH 8.0, 1% CHAPS and the inclusion body pellet washed and centrifuged. The washed inclusion body was solubilized with either 8M urea or 6M guanidine HCL containing 10mM Tris, pH 8.0, plus 10mM imidazole. The solubilized protein was then added to 5ml of nickel-chelate resin (Qiagen) and incubated for 45 minutes at room temperature.

Following the incubation, the resin and protein mixture was poured through a column and the flow through collected. The column was washed with 10-20 column volumes of buffer and the antigen eluted using 8M urea, 10mM Tris, pH 8.0, and 300 mM imidazole and collected in 3ml fractions. SDS-PAGE was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin was equilibrated with the appropriate buffer and the pooled fractions were loaded onto the column. Each antigen was eluted from the column with an increasing salt gradient. Fractions were collected and analyzed by a SDS-PAGE to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10mM Tris, pH 8.0, and the resulting protein was submitted for quality control for final release. The release criteria were: (a) purity as determined by SDS-PAGE or HPLC, (b) concentration as determined by Lowry assay or Amino Acid Analysis, (c) identity as determined by amino terminal protein, and (d) endotoxin levels as determined by the Limulus (LAL) assay. The proteins were then filtered through a 0.22µM filter and frozen until needed for immunizations.

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To generate polyclonal antisera, 400µg of O772P-1 or O772P-2 was combined with 100µg of muramyldipeptide (MDP). The rabbits were immunized every 4 weeks with 100µg of antigen mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animals were bled and sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

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To characterize the antisera, 96 well plates were coated with antigen followed by blocking with BSA. Rabbit sera was diluted in PBS and added to each well. The plates were then washed, and goat anti-rabbit horseradish peroxidase (HRP). The plates were again washed and TMB microwell Peroxidase Substrate was added. Following this incubation, the colormetric reaction was stopped and the plates read immediately at 450nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

Immunohistochemistry analysis of O772P expression was performed on paraffin-embedded formalin fixed tissue. O772P was found to be expressed in normal ovary and ovarian tumor, but not in normal heart, kidney, colon, lung or liver. Additionally, immunohistochemistry and flow cytometric analysis indicates that O772P is a plasma membrane-associated molecule. O772P contains 1 plasma transmembrane domain predicted to be encoded by amino acids 859-880. The N-terminus of O772P is extracellular and is encoded by amino acids 1-859, while the C-terminus is intracellular. Sequence analysis shows that there are 17 potential N-linked glycosylation sites.

#### **EXAMPLE 11**

#### O772P IS EXPRESSED ON THE SURFACE OF PRIMARY OVARIAN TUMOR CELLS

For recombinant expression in mammalian cells, the O772P-21008 (SEQ ID NO:387) and O772P full length cDNA (SEQ ID NO:311 encoding the protein of SEQ ID NO:312) were subcloned into mammalian expression vectors pBIB or pCEP4 respectively. These constructs were transfected into HEK293 cells using Fugene 6 (Roche). The HEK cells were then plated at a density of 100,000 cells/ml in DMEM containing fetal bovine serum (FBS) and grown overnight. The following day, 2µl of Fugene 6 was added to 100µl of DMEM, which contained no FBS, and incubated for 15 minutes at room temperature. The Fugene 6/DMEM mixture was then added to 1µg of O772P/pBIB or O772P/pCEP4 plasmid DNA and incubated for an additional 15 minutes at room temperature. The Fugene 6/DNA mix was then added to the HEK293 cells and incubated for 48-72 hours at 37°C with 7% CO<sub>2</sub>. The cells were rinsed and pelleted by centrifugation.

For Western Blot analysis, whole cell lysates were generated by incubating the cells in lysis buffer followed by clarification by centrifugation. The samples were diluted and run on SDS-PAGE. The gel was then transferred to nitrocellulose and probed using purified anti-O772P-2 rabbit polyclonal antibody. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate. Western Blot analysis revealed that O772P-21008 could be detected in HEK293 cells that had been transfected with O772P.

To determine the cell expression profile of O772P in cells, primary ovarian tumor cells were grown in SCID mice. The cells were retrieved from the mice and analyzed by flow cytometry. Briefly, cells washed in cold staining buffer containing PBS, 1% BSA, and Na Azide. The cells were incubated for 30 minutes with 10μg/ml of purified anti-O772P-1 and O772P-2 polyclonal sera. Following this incubation, the cells were washed three times in staining buffer and incubated with goat anti-rabbit Ig (H+L) conjugated to FITC (Southern Biotechnology). The cells were washed and resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that identifies non-viable cells. The cells were then analyzed using Fluorescence Activated Cell Sorting (FACS). FACS analysis revealed that O772P was present on the cells surface. Surface expression of O772P on tumor cells allows for immune targeting by therapeutic antibodies.

20 EXAMPLE 12

#### FUNCTIONAL CHARACTERIZATION OF ANTI-O8E MONOCLONAL ANTIBODIES

Mouse monoclonal antibodies (mAb) raised against E. coli derived O8E, as described in Example 8, were tested for their ability to promote O8E antigen internalization. Internalization of the antibody was determined using an in vitro cytotoxicity assay. Briefly, HEK293 and O8E/HEK transfected cells were plated into 96 well plates containing DME plus 10% heat-inactivated FBS in the presence of 50ng/well of purified anti-O8E or control antibodies. The isotype of the anti-O8E mAbs are as follows: 11A6-IgG1/kappa, 15C6-IgG2b/kappa, 18A8-IgG2b/kappa, and 14F1-IgG2a/kappa. W6/32 is a pan anti-human MHC class I mouse monoclonal antibody that serves as a positive control, and two irrelevant mAbs, Ir-Pharm and Ir-

Crxa were included as negative controls. Following incubation with the O8E specific antibodies or the relevant controls antibodies, the mAb-zap, a goat anti-mouse Igsaporin conjugated secondary antibody (Advanced Targeting Systems) was added at a concentration of 100ng/ml to half of the wells, and the plates were incubated for 48 to 72 hours at 37°C in a 7% CO<sub>2</sub> incubator. This assay takes advantage of the toxic nature of saporin, a ribozyme inactivating protein, which when internalized has a cytotoxic effect. Following incubation with the mAb-zap, internalization was quantitated by the addition of MTS reagent, followed by reading the OD490 of the plate on a microplate ELISA reader. Figure 25 depicts the results from these assays. The top panel represents HEK cells that have not been transfected with O8E and therefore O8E antibody should not bind and be internalized. Levels of proliferation were the same in all samples whether they were incubated with or without the mAb-zap, with the exception of the positive control Ab, W6/32. The lower panel represents cells that have been transfected with O8E and therefore should bind O8E specific antibodies. Antibodies from the hybridomas 11H6, 14F1, and 15C6, which recognize the amino acids 61-80 of O8E were able to promote internalization of the O8E surface protein as measured by decreased levels of proliferation due to the toxic nature of the mAb-zap (See Figure 25). The antibody generated by the hybridoma 18A8, which recognizes amino acids 151-170 of O8E, was unable to promote internalization as determined by normal levels of proliferation either in the absence or presence of the mAb-zap.

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#### **EXAMPLE 13**

#### CHARACTERIZATION OF THE OVARIAN TUMOR ANTIGEN, O772P

The cDNA and protein sequences for multiple forms of the ovarian tumor antigen O772P have been described in the above (e.g., Examples 2 and 9). A Genbank search indicated that O772P has a high degree of similarity with FLJ14303 (Accession # AK024365; SEQ ID NO:457 and 463). Protein sequences corresponding to O772P and FLJ14303 are disclosed in SEQ ID NO:478 and 479, respectively. FLJ14303 was identical to the majority of O772P, with much of the 3'-end showing 100% homology. However, the 5'-end of FLJ14303 was found to extend further 5' than O772P. In addition, FLJ14303 contained a 5 bp insert (SEQ ID NO:457) resulting in a

frame shift of the amino-terminus protein sequence such that FLJ14303 utilizes a different starting methionine than O772P and therefore encodes a different protein. This insertion was present in the genomic sequence and seen in all EST clones that showed identity to this region, suggesting that FLJ14303 (SEQ ID NO:457) represents a splice variant of O772P, with an ORF that contains an extended and different amino-terminus. The additional 5'-nucleotide sequence included repeat sequences that were identified during the genomic mapping of O772P. The 5'-end of O772P and the corresponding region of FLJ14303 showed between 90-100% homology. Taken together, this suggests that O772P and FLJ14303 are different splice variants of the same gene, with different unique repeat sequences being spliced into the 5'-end of the gene.

The identification of an additional ten or more repeat sequences within the same region of chromosome 19, indicates that there may be many forms of O772P, each with a different 5'-end, due to differential splicing of different repeat sequences. Northern blot analysis of O772P demonstrated multiple O772P-hybridizing transcripts of different sizes, some in excess 10kb.

Upon further analysis, 13 additional O772P-related sequences were identified, the cDNA and amino acid sequences of which are described in Table 2.

Table 2

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SEQ ID NO:	Description	Transmembrane Domains
464	LS #1043400.1 (cDNA)	nd
465	LS #1043400.10 (cDNA)	0
466	LS #1043400.11 (cDNA)	2
467	LS #1043400.12 (cDNA)	2
468	LS #1043400.2 (cDNA)	nd
469	LS #1043400.3 (cDNA)	
470	LS #1043400.5 (cDNA)	nd
471	LS #1043400.8 (cDNA)	1
472	LS #1043400.9 (cDNA)	0

	<del></del>	
473	LS #1043400.6 (cDNA)	nd
474	LS #1043400.7 (cDNA)	nd
475	LS #1043400.4 (cDNA)	nd
476	LS #1397610.1 (cDNA)	0
477	1043400.10 Novel 5' (cDNA)	-
480	LS #1043400.9 (amino acid)	-
481	LS #1043400.8B (amino acid)	-
	Contains a transmembrane	
	domain	
482	LS #1043400.8A (amino acid)	-
483	LS #1043400.12 (amino acid)	- ,
	Contains a transmembrane	
	domain	
484	LS #1043400.11B (amino acid)	-
	Contains a transmembrane	·
	domain	
485	LS #1043400.11A (amino acid)	
486	LS #1043400.10 (amino acid)	-
487	LS #1043400.1 (amino acid)	

#### nd=not determined

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Initially it appeared that these sequences represented overlapping and/or discrete sequences of O772P splice forms that were capable of encoding polypeptides unique to the specific splice forms of O772P. However, nucleotide alignment of these sequences failed to identify any identical regions within the repeat elements. This indicates that the sequences may represent different specific regions of a single O772P gene, one that contains 16 or more repeat domains, all of which form a single linear transcript. The 5'-end of sequence LS #1043400.10 (Table 2; SEQ ID NO:465) is unique to both O772P and FLJ14303 and contains no repeat elements, indicating that this sequence may represent the 5'-end of O772P.

Previously, transmembrane prediction analysis had indicated that O772P contained between 1 and 3 transmembrane spanning domains. This was verified by the

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use of immunohistochemistry and flow cytometry, which demonstrated the existence of a plasma membrane-associated molecule representing O772P. However, immunohistochemistry also indicated the presence of secreted form(s) of O772P, possibly resulting from an alternative splice form of O772P or from a post-translational cleavage event. Analysis of several of the sequences presented in Table 2 showed that sequences 1043400B.12, 1043400.8B, and 1043400.11B all contained transmembrane regions, while 1043400.8A, 1043400.10, 1043400.1, 1043400.11A, and 1043400.9 were all lacking transmembrane sequences, suggesting that these proteins may be secreted.

Analysis indicates a part of O772P is expressed and/or retained on the plasma membrane, making O772P an attractive target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. The predicted extracellular domain of O772P is disclosed in SEQ ID NO:489 and secretion of O772P is likely to occur as a result of a cleavage event within the sequence:

SLVEQVFLD<u>K</u>TLNASFHWLGSTYQLVDIHVTEMESSVYQP.

Proteolytic cleavage is most likely to occur at the Lysine (K) at position 10 of SEQ ID NO:489. The extracellular, transmembrane, and cytoplasmic regions of O772P are all disclosed in SEQ ID NO:488:

Extracellular:

SLVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVYQPTSSSS
TQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQTFRNSSIKSYFSDCQ
VSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDR
SSYLVDGYFPNRNEPLTGNSDLPF

Transmembrane:

WAVILIGLAGLLGLITCLICGVLVTT

Cytoplasmic:

RRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

#### **EXAMPLE 14**

## IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS OF O8E EXPRESSION IN OVARIAN CANCER AND NORMAL TISSUES

In order to determine which tissues express the ovarian cancer antigen O8E, IHC analysis was performed on a diverse range of tissue sections using both polyclonal and monoclonal antibodies specific for O8E. The generation of O8E specific polyclonal antibodies is described in detail in Example 8. The monoclonal antibodies used for staining were 11A6 and 14F1, both of which are specific for amino acids 61-80 of O8E and 18A8, which recognizes amino acids 151-170 of O8E (see Example 12 for details on generation).

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To perform staining, tissue samples were fixed in formalin solution for 12-24 hours and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope retrieval (SHEIR) in 0.1M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody was then added to each section for 25 minutes followed by 25 minutes of incubation with either anti-rabbit or anti-mouse biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize the antigen expression. Slides were counterstained with hematoxylin to visualize the cell nuclei.

Results using rabbit affinity purified polyclonal antibody to O8E (a.a. 29-283; for details on the generation of this Ab, see Example 3) are presented in Table 3. Results using the three monoclonal antibodies are presented in Table 4.

<u>Table 3</u>
<u>Immunohistochemistry analysis of O8E using polyclonal antibodies</u>

Tissue	O8E Expression	
Ovarian Cancer	Positive	
Breast Cancer	Positive	

Normal Ovary	Positive	
Normal Breast	Positive	
Blood Vessel	Positive	
Kidney	Negative	
Lung	Negative	
Colon	Negative	
Liver	Negative	
Heart	Negative	

<u>Table 4</u>
<u>Immunohistochemistry analysis of O8E using monoclonal antibodies</u>

Normal	11A6		18A8		14F1	
Tissue	Endothelia	Epithelial	Endothelial	Epithelial	Endothelial	Epithelial
	1 .	,				
Skin	2	2	0	0	1	1
Skin	1	1	0	0	1	1 .
Breast	0	1	n/a	n/a	1	1
Colon	0	0	0	o	0	0
Jejunum	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Ovary	0	0	0	0	1	0 .
Colon	0	0	0	0	0	1
Liver	0	0	0	0	1	2
Skin	0	0	0	0	1	0
Duodenum	0	0	0	0	0	0
and Pancreas						
Appendix	0	0	0	0	0	0
Ileum	0	0	0	0	0	0

0=no staining, 1=light staining, 2=moderate staining, n/a=not available

## EXAMPLE 15 EPITOPE MAPPING OF O772P POLYCLONAL ANTIBODIES

To perform epitope mapping of O772P, peptides were generated, the sequences of which were derived from the sequence of O772P. These peptides were 15 5 mers that overlapped by 5 amino acids and were generated via chemical synthesis on membrane supports. The peptides were covalently bound to Whatman 50 cellulose support by their C-terminus with the N-terminus unbound. In order to determine epitope specificity, the membranes were wet with 100% ethanol for 1 minute, and then blocked for 16 hours in TBS/Tween/Triton buffer (50mM Tris, 137 mM NaCl, 2.7 mM KCl, 0.5% BSA, 0.05% Tween 20, 0.05% Triton X-100, pH 7.5). The peptides were then probed with 2 O772P specific antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312; see Example 10 for details of antibody generation), as well as irrelevant rabbit antibodies for controls. The antibodies were diluted to 1µg/ml and incubated with the membranes for 2 hours at room temperature. The membranes were then washed for 30 minutes in TBS/Tween/Triton buffer, prior to being incubated with a 1:10,000 dilution of HRP-conjugated anti-rabbit secondary antibody for 2 hours. The membranes were again washed for 30 minutes in TBS/Tween/Triton and anti-peptide reactivity was visualized using ECL. Specific epitope binding specificity for each of the O772P-polyclonal antibodies is described in

Table 5

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Table 5.

SEQ ID NO:	Peptide #	Anti-O772P1	Anti-O772P2	Peptide Sequence
490	2	***	-	TCGMRRTCSTLAPGS
491	6	*	*/-	CRLTLLRPEKDGTAT
492	7	*	-	DGTATGVDAICTHHP
493	8		-	CTHHPDPKSPRLDRE
494	9	***	***	RLDREQLYWELSQLT
495	11	*/-		LGPYALDNDSLFVNG
496	13	****	-	SVSTTSTPGTPTYVL
497	22	<u> </u>	-	LRPEKDGEATGVDAI
498	24	**	*/-	DPTGPGLDREQLYLE
499	27	*/-		LDRDSLYVNGFTHRS
500	40	*/-	-	GPYSLDKDSLYLNGY
501	41	-	-	YLNGYNEPGPDEPPT
502	47	***	***	ATFNSTEGVLQHLLR

503	50	-	***	QLISLRPEKDGAATG
504	51	-	**	GAATGVDTTCTYHPD
505	52		*/-	TYHPDPVGPGLDIQQ
506	53	-	*	LDIQQLYWELSQLTH
507	58	-	*	HIVNWNLSNPDPTSS
508	59	-	*	DPTSSEYITLLRDIQ
509	60	-	*	LRDIQDKVTTLYKGS
510	61	-	***	LYKGSQLHDTFRFCL
511	71	-	**	DKAQPGTTNYQRNKR

<sup>\*=</sup> relative reactive level, -; no binding, \*\*\*\*; maximal binding

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# EXAMPLE 16 IDENTIFICATION OF A NOVEL N-TERMINAL REPEAT STRUCTURE ASSOCIATED WITH O772P

Various O772P cDNA and protein forms have been identified and characterized as detailed above (e.g., Examples 1, 2, 9, and 14). Importantly, O772P RNA and protein have been demonstrated to be over-expressed in ovarian cancer tissue relative to normal tissues and thus represents an attractive target for ovarian cancer diagnostic and therapeutic applications.

Using bioinformatic analysis of open reading frames (ORFs) from genomic nucleotide sequence identified previously as having homology with O772P, multiple nucleotide repeat sequences were identified in the 5' region of the gene encoding the O772P protein. A number of these repeat sequences were confirmed by RT-PCR using primers specific for the individual repeats. Fragments which contained multiple repeats were amplified from cDNA, thus confirming the presence of specific repeats and allowing an order of these repeats to be established.

Unexpectedly, when various sets of O772P sequences derived from different database and laboratory sources were analyzed, at least 20 different repeat structures, each having substantial levels of identity with each other (see Table 6), were identified in the 5' region of the O772P gene and the corresponding N-terminal region of the O772P protein. Each repeat comprises a contiguous open reading frame encoding a polypeptide unit that is capable of being spliced to one or more other repeats such that concatomers of the repeats are formed in differing numbers and orders. Interestingly, other molecules have been described in the scientific literature that have repeating structural domains analogous to those described herein for O772P. For example, the

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mucin family of proteins, which are the major glycoprotein component of the mucous which coats the surfaces of cells lining the respiratory, digestive and urogenital tracts, have been shown to be composed of tandemly repeated sequences that vary in number, length and amino acid sequence from one mucin to another (Perez-Vilar and Hill, *J. Biol. Chem. 274(45)*:31751-31754, 1999).

The various identified repeat structures set forth herein are expected to give rise to multiple forms of O772P, most likely by alternative splicing. The cDNA sequences of the identified repeats are set forth in SEQ ID NOs:513-540, 542-546, and 548-567. The encoded amino acid sequences of the repeats are set forth in SEQ ID NOs:574-593. In many instances these amino acid sequences represent consensus sequences that were derived from the alignment of more than one experimentally derived sequence.

Each of these splice forms is capable of encoding a unique O772P protein with multiple repeat domains attached to a constant carboxy terminal protein portion of O772P that contains a trans membrane region. The cDNA sequence of the O772P constant region is set forth in SEQ ID NO:568 and the encoded amino acid sequence is set forth in SEQ ID NO:594.

All of the available O772P sequences that were obtained were broken down into their identifiable repeats and these sequences were compared using the Clustal method with weighted residue weight table (MegAlign software within DNASTAR sequence analysis package) to identify the relationship between the repeat sequences. Using this information, the ordering data provided by the RT-PCR, and sequence alignments (automatic and manual) using SeqMan (DNASTAR), one illustrative consensus full length O772P contig was identified comprising 20 distinct repeat units. The cDNA for this O772P cDNA contig is set forth in SEQ ID NO:569 and the encoded amino acid sequence is set forth in SEQ ID NO:595. This form of the O772P protein includes the following consensus repeat structures in the following order:

SEQ ID NO:572- SEQ ID NO:574- SEQ ID NO:575-SEQ ID NO:576-30 SEQ ID NO:577- SEQ ID NO:578- SEQ ID NO:589- SEQ ID NO:580- SEQ ID NO:581- SEQ ID NO:582- SEQ ID NO:583- SEQ ID NO:584- SEQ ID NO:585- SEQ

ID NO:586- SEQ ID NO:587- SEQ ID NO:588- SEQ ID NO:589- SEQ ID NO:590- SEQ ID NO:591- SEQ ID NO:592- SEQ ID NO:593.

SEQ ID NO:595, therefore, represents one illustrative full-length consensus sequence for the O772P protein. As discussed above, however, based on current knowledge of this protein and based upon scientific literature describing proteins containing analogous repeating structures, many other forms of O772P are expected to exist with either more or less repeats. In addition, many forms of O772P are expected to have differing arrangements, e.g., different orders, of these N-terminal repeat structures. The existence of multiple forms of O772P having differing numbers of repeats is supported by Northern analysis of O772P. In this study, Northern hybridization of a O772P-specific probe resulted in a smear of multiple O772P-hybridizing transcripts, some in excess 10kb.

Thus, the variable repeat region of the O772 protein can be illustratively represented by the structure Xn – Y, wherein X comprises a repeat structure having at least 50% identity with the consensus repeat sequence set forth in SEQ ID NO:596; n is the number of repeats present in the protein and is expected to typically be a integer from 1 to about 35; Y comprise the O772P constant region sequence set forth in SEQ ID NO:594 or sequences having at least 80% identity with SEQ ID NO:594. Each X present in the Xn repeat region of the O772 molecule is different.

To determine the consensus sequences of each of the 20 repeat regions, sequences that were experimentally determined for a discrete repeat region were aligned and a consensus sequence determined. In addition to determining the consensus sequences for individual repeat regions, a consensus repeat sequence was also determined. This sequence was obtained by aligning the 20 individual consensus sequences. Variability of the repeats was determined by aligning the consensus amino acid sequences from each of the individual repeat regions with the over all repeat consensus sequence. Identity data is presented in Table 6.

<u>Table 6</u>

<u>Percent identities of Repeat Sequences with Reference to the Consensus Repeat Sequence</u>

Repeat Number	SEQ ID NO:	Percent Identity to
(amino acid)		Consensus Repeat
		Sequence
2	574	88
3	575	84
4	. 576	88
5	577	89
6	578	93
7	579	90
8	580	91
9	581	88
10	582	85
11	583	86
12	. 584	87
13	585	87
14	586	89
15	587	89
16	588	89
17	589	83
18	590	84
19	591	83
20	592	57
21	593	68

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,

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various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

#### **CLAIMS**

#### What is Claimed:

1. An O772P polypeptide having the structure:

 $X_{n}-Y$ 

wherein X comprises a sequence having at least 50% identity with the consensus O772P repeat sequence set forth in SEQ ID NO: 596;

Y comprises a sequence having at least 80% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 2. The polypeptide of claim 1, wherein X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593.
- 3. The polypeptide of claim 1, wherein Y comprises the sequence set forth in SEQ ID NO: 594.
  - 4. The polypeptide of claim 1, wherein n is an integer from 15 to 25.
  - 5. The polypeptide of claim 1, wherein n is 20.
- 6. The polypeptide of claim 1, wherein said polypeptide comprises SEQ ID NO: 595.
- 7. The polypeptide of claim 1, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
  - 8. An O772P polypeptide having the structure:

 $X_{n}-Y$ 

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 574-593;

Y comprises a sequence having at least 90% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 15 to 25;

wherein each X present in said polypeptide is different.

- 9. The polypeptide of claim 8, wherein n is 20.
- 10. The polypeptide of claim 8, wherein said polypeptide comprises SEQ ID NO: 595.
- 11. The polypeptide of claim 8, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
  - 12. An O772P polypeptide having the structure:

 $X_{n}-Y$ 

wherein n is 20 and X comprises the following O772P repeat sequences:

SEQ ID NO: 574 - SEQ ID NO: 575 - SEQ ID NO: 576 - SEQ ID NO:

577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ

ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO:

586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ

ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593; and

Y comprises the sequence set forth in SEQ ID NO: 594.

- 13. The polypeptide of claim 12, wherein said polypeptide comprises SEQ ID NO: 595.
- 14. The polypeptide of claim 12, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.

15. An O772P polynucleotide having the structure:

 $X_n-Y$ 

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567;

Y comprises a sequence having at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 16. The polynucleotide of claim 15, wherein said polynucleotide comprises SEQ ID NO: 569.
  - 17. The polynucleotide of claim 15, wherein n is from 15 to 25.
  - 18. The polynucleotide of claim 15, wherein n is 20.
- 19. The polynucleotide of claim 15, wherein said polynucleotide is overexpressed in ovarian cancer cells compared with normal tissues.
- 20. An isolated polynucleotide comprising a sequence selected from the group consisting of:
  - (a) sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (b) complements of the sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs: 464-477 and 512-569;
- (d) sequences that hybridize to a sequence provided in SEQ ID NOs: 464-477 and 512-569, under highly stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NOs: 464-477 and 512-569:

- (f) sequences having at least 90% identity to a sequence of SEQ ID NOs: 464-477 and 512-569; and
- (g) degenerate variants of a sequence provided in SEQ ID NOs: 464-477 and 512-569.
- 21. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of: '
  - (a) sequences encoded by a polynucleotide of claim 20; and
- (b) sequences having at least 80% identity to a sequence encoded by a polynucleotide of claim 20; and
- (c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 20.
- 22. An expression vector comprising a polynucleotide of claim 20 operably linked to an expression control sequence.
- 23. A host cell transformed or transfected with an expression vector according to claim 22.
- 24. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 21.
- 25. A method for detecting the presence of a cancer in a patient, comprising the steps of:
  - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 21;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

- 26. A fusion protein comprising at least one polypeptide according to claim 21.
- 27. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
  - (a) polypeptides according to claim 21;
  - (b) polynucleotides according to claim 20; and
- (c) antigen-presenting cells that express a polynucleotide according to claim 20,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 28. An isolated T cell population, comprising T cells prepared according to the method of claim 27.
- 29. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:
  - (a) polypeptides according to claim 21;
  - (b) polynucleotides according to claim 20;
  - (c) antibodies according to claim 24;
  - (d) fusion proteins according to claim 26;
  - (e) T cell populations according to claim 28; and
- (f) antigen presenting cells that express a polypeptide according to claim 21.
- 30. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 29.

- 31. A method for the treatment of a ovarian cancer in a patient, comprising administering to the patient a composition of claim 29.
- 32. A method for determining the presence of a cancer in a patient, comprising the steps of:
  - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide that hybridizes to a polynucelotide sequence according to claim 21 under moderately stringent conditions;
- (c) detecting in the sample an amount of said polynucleotide that hybridizes to the oligonucleotide; and
- (d) comparing the amount of said polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.
- 33. An O772 polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.
- 34. An O8E polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.
- 35. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 1.

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#### 11729.1 contg

#### 11729-45.21.21.cons1

#### 11729-45.21.21.cons2

#### 11731.1contig

## Fig. 1A

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#### 11731.2contig

#### 11734.1contig

AATAGATTTAATGCAGAGTGTCAACTTCAATTGATTGATAGTGGCTGCCTAGAGTGCTGTTGTTGAGTAGGTTTC
TGAGGATGCACCCTGGCTTGAAGAGAAAGACTGGCAGGATTAACAATATCTAAAATCTCACTTGTAGGAGAAAC
CACAGGCACCAGAGCTGCCACTGGTGCTGGCACCAGGCCCACCAAGGCCAGCGAAGAGCCCAAATGTGAGAGTG
GCGGTCAGGCTGGCACCAGCACTGAAGCCACCACTGGTGCTGGCACTGGCACTGGCACTGTTATTGGTACTGGT
ACTGGCACCAGTGCTGGCACTGCCACTCTCTTGGGCTTTGGCTTTAGCTTCTGCTCCCGCCTGGATCCGGGCTT
TGGCCCAGGGTCCGATATCAGCTTCGTCCCAGTTGCAGGCCCGGCAGCATTCTCCGAGCCGAGCCCAATGCCC
ATTCGAGCTCTAATCTCGGCCCTAGCCTTGGCTTCAGCTGCAGCCTCAGCTTCCAAATCCGCTTCCAT
CGCCTCTCGGTAC

#### 11734.2contig

GCCAAGAAAGCCCGAAAGGTGAAGCATCTGGATGGGGAAGAGGATGGCAGCAGTGATCAGAGTCAGGCTTCTGG
AACCACAGGTGGCCGAAGGGTCTCAAAGGCCCTAATGGCCTCAATGGCCCGCAGGGCTTCAAGGGGTCCCATAG
CCTTTTGGGCCCGCAGGGCATCAAGGACTCGGTTGGCTGCTTTGGGCCCGGAGAGCCTTGCTCTCCCTGAGATCA
CCTAAAGCCCGTAGGGGCAAGGCTCGCCGTAGAGCTGCCAAGCTCCAGTCATCCCAAGAGCCTGAAGCACCACC
ACCTCGGGATGTGGCCCTTTTGCAAGGGAGGGCAAATGATTTGGTGAAGTACCTTTTTGGCTAAAGACCAGACGA
AGATTCCCATCAAGCGCTCGGACATGCTGAAGGACATCATCAAAGAATACACTGATGTGTACCCCGAAATCATT
GAACGAGCAGGCTATTCCTTGGAGAAAGGTATTTGGGATTCAATTGAAGGAAATTGATAAGAATGACCACTTGTA
CATTCTTCTCAGC

#### 11736.1contg

Fig. 1B

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#### 11736.2contig

#### 11739-182

#### 11740.1.contig

## Fig. 1C

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#### 11766.1.contig

#### 11766.2.contig

#### 11773.2. contig

#### 11775-1&2

## 5/101 11777.1&2.cons

#### 11779.2.contig

#### 11781 & 37.cons

Fig. 1E

## 6/101 11781-76-87-37

#### 11784-1 & 2

#### 11785.2.contig

## Fig. 1F

## 7/101 11718-1&2 cons

#### 13690.4

CAACTTATTACTTGAAATTATAATATAGCCTGTCCGTTTGCTGTTTCCAGGCTGTGATATATTTTCCTAGTGGTTTGACTTTAAAAATAAAGGTTTAATTTTCTCCCC

#### 13693.1

#### 13694.1

CAGAGAATCTKAGAAAGATGTCGCGTTTTCTTTTAATGAATGAGAGAAGCCCATTTGTATCCCTGAATCATTGA
GAAAAGGCGGCGGCGACAGCGGCGACCTAGGGATCGATCTGGAGGACCTTTGGGGAGCGTGCAGAGACCTCT
AGCTCGAGCGCGAGGGACCTCCCGCCGGGATGCCTGGGGAGCAGATGGACCCTACTGGAAGTCAGTTGGATTCA
GATTTCTCTCAGCAAGATACTCCTTGCCTGATAATTGAAGATTCTCAGCCTGAAAGCCAGGTTCTAGAGGATGA
TTCTGGTTCTCACTTCAGTATGCTATCTCGACACCTTCCTAATCTCCAGACGCACAAAGAAAATCCTGTGTTGG
ATGTTGNGTCCAATCCTTGAACAAACAGCTGGAGAAGAACCGAGGAGACCGGTAATAGTGGGTTCAATGAACATT
TGAAAGAAAACCAGGTTGCAGACCCTG

Fig. 1G

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#### 13694.2

GACTGTCCTGAACAAGGGACCTCTGACCAGAGAGCTGCAGGAGATGCAGAGTGGCAGGAGTGGAAGCCAAA
GAACACCCACCTTCCTCCCTTGAAGGAGTAGAGCAACCATCAGAAGATACTGTTTTATTGCTCTGGTCAAACAA
GTCTTCCTGAGTTGACAAAACCTCAGGCTCTGGTGACTTCTGAATCTGCAGTCCACTTTCCATAAGTTCTTGTG
CAGACAACTGTTCTTTTGCTTCCATAGCAGCAACAGATGCTTTGGGGCTAAAAGGCATGTCCTTGACCTTGCA
GGTGGTGGATTTTGCTCTTTTACAACATGTACATCCTTACTGGGCTGTGCTGTCACAGGGATGTCCTTGCTGGA
CTGTTCTGCTATGGGGATATCTTCGTTGGACTGTTCTTCATGCTTAATTGCAGTATTAGCATCCACATCAGACA
GCCTGGTATAACCAGAGTTGGTGGTTACTGATTGTAGCTGCTCTTTTGTCCACTTCATATGGCACAAGTATTTTC
CTCAACATCCTGGCTCTGGGAAG

#### 13695.1

GAAATGTATATTTAATCATTCTCTTGAACGATCAGAACTCTRAAATCAGTTTTCTATAACARCATGTAATACAG
TCACCGTGGCTCCAAGGTCCAGGAAGGCAGTGGTTAACACACATGAAGAGTGTGGGAAGGGGGCCTGGAAACAAAGT
ATTCTTTTCCTTCAAAGCTTCATTCCTCAAGGCCTCAATTCAAGCAGTCATTGTCCTTGCATTCAAAAGTCTGT
GTGTGCTTCATGGAAGGTATATGTTTGTTGCCTTAATTTGAATTGTGGCCAGGAAGGGTCTGGAGATCTAAATT
CAGAGTAAGAAAACCTGAGCTAGAACTCAGGCATTTCTCTTACAGAACTTGGCTTGCAGGGTAGAATGAANGGA
AAGAAACTTAGAAGCTCAACAAGCTGAAGATAATCCCATCAGGCATTTCCCATAGGCCTTGCAACTCTGTTCAC
TGAGAGATGTTATCCTG

#### 13695.2

#### 13697.1

TAGCTGTCTTCCTCACTCTTATGGCAATGACCCCCATATCTTAATGGATTAAGATAATGAAAGTGTATTTCTTAC ACTCTGTATCTATCACCAGAAGCTGAGGTGATAGCCCGCTTGTCATTGTCATCCATATTCTGGGACTCAGGCGG GAACTTTCTGGGAATATTGCCAGGGAGCATGGCAGAGGCACAGTGCATTCTGGGGAATGCACAATTGCCCAGGAGCACCAACCCCAAATGAGTGATATACATTACCTCTGTTCACAACTCATTGCCCAGCACCAAATCCCAAAATGTAGTCCTGTTGATATGGTTTTGCTGTGTCCCAACCCAAATCTCATCTTGAATTGT AAGCTCCCATAATTCCCATGTGTTGTGGGAGGGACCTGGTG

## Fig. 1H

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#### 13697.2

#### 13699.1&2

#### 13703.3

#### 13705.1

## Fig. 11

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#### 13705.2

#### 13707.4

#### 13708.182

GGCGGGTAGGCATGGAACTGAGAAGAACGAAGAAGCTTTCAGACTACGTGGGGAAGAATGAAAAAACCAAAATT
ATCGCCAAGATTCAGCAAAGGGGACAGGGAGCTCCAGCCCGAGAGCCTATTATTAGCAGTGAGGAGCAGAAGCA
GCTGATGCTGTACTATCACAGAAGACAAGAGAGAGCTCAAGAGATTGGAAGAAAATGATGATGATGCCTATTTAA
ACTCACCATGGGCGGATAACACTGCTTTGAAAAGACATTTTCATGGAGTGAAAGACATAAAGTGGAGACCAAGA
TGAAGTTCACCAGCTGATGACACTTCCAAAGAGATTAGCTCACCT

#### 13709.1

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#### 13709.2

TATGAAGAAGGGAAAAGAAGATAATTTGTGAAAGAAATGGGTCCAGTTACTAGTCTTTGAAAAGGGTCAGTCTG
TAGCTCTTCTTAATGAGAATAGGCAGCTTTCAGTTGCTCAGGGTCAGATTTCCTTAGTGGTGTATCTAATCACA
GGAAACATCTGTGGTTCCCTCCAGTCTCTTTCTGGGGGGACTTGGGCCCACTTCTCATTTCATTTAATTAGAGGA
AATAGAACTCAAAGTACAATTTACTGTTGTTTAACAATGCCACAAAGACATGGTTGGGAGCTATTTCTTGATTT
GTGTAAAATGCTGTTTTTTGTGTGCTCCATAATGGTTCCAAAAATTGGGTGCTGCCCAAAGAGAGATACTGTTACA
GAAGCCAGCAAGAAGACCTCTGTTCATTCACACCCCCCGGGGATATCAGGAATTGACTCCAGTGTGTGCAAAATCC
AGTTTGGCCTATCTTCT

#### 13712.1&2

#### 13714.1&2

#### 13716.1&2

## Fig. 1K

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#### 13718.2

#### 13722.3

CATGCGTTTCACCACTGTTGGCCAGGCTGGTCTCGAACTCCTGGCCTCAAGCAATCCACCCGCCTCAGCCTCCA
AAAGTGCTGGGATTACAGATGTGAGCCATGGCACCATGCCAAAAGGCTATATTCCTGGCTCTGTTTTCCGAGA
CTGCTTTTAATCCCAACTTCTCTACATTTAGATTAAAAAAATATTTTTATTCATGGTCAATCTGGAACATAATTAC
TGCATCTTAAGTTTCCACTGATGTATATAAGAAGGCTAAAGGCACAATTTTTATCAAATCTAGTAGAGTAACCAA
ACATAAAATCATTAATTACTTTCAACTTAATAACTAATTGACATTCCTCAAAAGAGCTGTTTTCAATCCTGATA
GGTTCTTTATTTTTTCAAAATATATTTGCCATGGGATGCTAATTTGCAATAAGGCGCATAATGAGAATACCCCA
AACTGGA

#### 13722.4

#### 13724-13698-13748

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#### 13730.1

#### 13732.1

ATGATCTTACTTTGCCACCCAGGTTGGAGTGCAGTGCTGCAATCTTGGCTCACTGCAGCCTTAACCTCCCAGG
CTCAAGCTATCCTCCTGCCAAAGCCTTCCACATAGCTGGGACTACAGGTACACNGCCACCACACCCAGGCTAAAA
TTTTTGTATTTTTTTGTAGAGACCGGGATCTCGCCACGTTGCCCAGGCTGGTCCCATCCTGACCTCAAGCAGATCT
GCCCACCTCAGCCCCCCAACGTGCTAGGATTACAGGCGTGAGCCACCGCACCCAGCCTTTGTTTTGCTTTTAAT
GGAATCACCAGTTCCCCTCCGTGTCTCAGCAGCAGCTGTGAGAAATGCTTTGCATCTGTGACCTTTATGAAGGG
GAACTTCCATGCTGAATGAGGGTAGGATTACATGCTCCTGTTTCCCGGGGGTCAAGAAAGCCTCAGACTCCAGC
ATGATAAGCAGGGTGAG

#### 13732.2

Fig. 1M

## 14/101 13735.1

#### 13735.2

#### 13736.1

#### 13737.182

Fig. 1N

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## 13738.1

TTTGACTTTAGTAGGGGTCTGAACTATTTATTTTACTTTGCCMGTAATATTTARACCYTATATATCTTTCATTA
TGCCATCTTATCTTCTAATGBCAAGGGAACAGWTGCTAAMCTGGCTTCTGCATTWATCACATTAAAAATGGCTT
TCTTGGAAAATCTTCTTGATATGAATAAAGGATCTTTTAVAGCCATCATTTAAAGCMGGNTTCTCTCCAACACG
AGTCTGCTSASGGGGGKGAGCTGTGAACTCTGGCTGAAGGCTTTCCCATACACACTGCAATGACMTGGTTTCT
GACCAGBGTGAGTTA

## 13738.2

## 13739.1&2

#### 13741.1

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## 13742.1

## 14351.1

## 14351.2

ACCTTAAAGACATAGGAGAATTTATACTGGGAGAGAAAGCTTACAAATGTAAGGTTTCTGACAAGACTTGGGAG TGATTCACACCTGGAACAACATACTGGACTTCACACTGGABAGAAACCTTACAAGTGTAATGAGTGTGGCAAAG CCTTTGGCAAGCAGTCAACACTTATTCACCATCAGGCAATTCA

#### 14354.2

AGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGGCCAAATATGTGGGCTATTACATCTGAAG
AACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGGAGGTTACATAACAGGTGATCAAGCCCGT
ACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAATATGGGCCCTTATCAGATCTGAACAAGGA
TGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATCAAGTTAAAGTTGCAGGGCCAACAGCTGC
CTGTAGTCCTCCCTCCTATCATGAAACAACCCCCTATGTTCTCCCACTAATCTCTGCTCGTTTTTGGGATGGGA
AGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCACCTATAGCAACACCCCTTGTCTTCTGCTAC
TTCAGGGACCAGTATTCCTCCCTAATGATGCCTGCT

#### 14354.1

# Fig. 1P

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## 16431.1.2

#### 16432-1

#### 16432-2

## 17184.3

# Fig. 1Q

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## 17184.4

CAAGCGTTCCTTTATGGATGTAAATTCAAACAGTCATGCTGAGCCATCCCGGGCTGACAGTCACGTTWAAGACA CTAGGTCGGGCGCCACAGTGCCACCCAAGGAGAAGAAGAATTTTGGAATTTTTCCATGAAGATGTACGGAAATCT GATGTTGAATATGAAAATGGCCCCCAAATGGAATTCCAAAAGGTTACCACAGGGGGCTGTAAGACCTAGTGACCC TCCTAAGTGGGAAAGAGGAATGGAGAATAGTATTTCTGATGCATCAAGAACATCAGAATATAAAACTGAGATCA TAATGAAGGAAAATTCCATATCCAATATGAGTTTACTCAGAGACAGTAGAAACTATTCCCAGG

## 17185.1

TAGGAATAACAAATGTTTATTCAGAAATGGATAAGTAATACATAATCACCCTTCATCTCTTAATGCCCCTTCCT
CTCCTTCTGCACAGGAGACACAGATGGGTAACATAGAGGCATGGGAAGTGGAGGAGGACACAGGACTAGCCCAC
CACCTTCTCTCCCGGTCTCCCCAAGATGACTGCTTATAGAGTGGAGGAGGCAAACAGGTCCCCTCAATGTACCA
GATGGTCACCTATAGCACCAGCTCCAGATGGCCACGTGGTTGCAGCTCGACTCAATGAAACTCTGTGACAACCA
GAAGATACCTGCTTTGGGATGAGAGGGAGGATAAAAGCCATGCAGGAGGATATTTACCATCCCTACCCTAAGCA
CAGTGCAAGCAGTGAGCCCCCGGCTCCCAGTACCTGAAAAACCAAGGCCTACTGNCTTTTGGATGCTCTCTTGG
GCCACG

#### 17188.2

#### 17190.1

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## 17190.2

## 17191.2889.2

Fig. 1S

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AGCCAGATGGCTGAGAGCTGCAAGAAGAAGTCAGGATCATGATGGCTCAGTTTCCCCACAGCGATGAATGGAGGG CCAAATATGTGGGCTATTACATCTGAAGAACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGG AGGTTACATAACAGGTGATCAAGCCCGTACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAA TATGGGCCTTATCAGATCTGAACAAGGATGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATC ACTAATCTCTGCTCGTTTTTGGGATGGGAAGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCAC CTATAGCAACACCCTTGTCTTCTGCTACTTCAGGGACCAGTATTCCTCCCCTAATGATGCCTGCTCCCCTAGTG CCTTCTGTTAGTACATCCTCATTACCAAATGGAACTGCCAGTCTCATTCAGCCTTTATCCATTCCTTATTCTTC TTCAACATTGCCTCATGCATCATCTTACAGCCTGATGATGGGAGGATTTGGTGGTGCTAGTATCCAGAAGGCCC AGTCTCTGATTGATTTAGGATCTAGTAGCTCAACTTCCTCAACTGCTTCCCTCTCAGGGAACTCACCTAAGACA GGGACCTCAGAGTGGGCAGTTCCTCAGCCTTCAAGATTAAAGTATCGGCAAAAATTTAATAGTCTAGACAAAGG CTACTATTTGGACTCTGGCTGACATCGATGGTGACGGCACAGTTGAAAGCTGAAGAATTTATTCTGGCGATGCAC CTCACTGACATGGCCAAAGCTGGACAGCCACTACCACTGACGTTGCCTCCCGAGCTTGTCCCTCCATCTTTCAG AGGGGGAAAGCAAGTTGATTCTGTTAATGGAACTCTGCCTTCATATCAGAAAACACAAGAAGAAGAAGACCTCAGA AGAAACTGCCAGTTACTTTTGAGGACAAACGGAAAGCCAACTATGAACGAGGAAACATGGAGCTGGAGAAGCGA GAAACAGAGAGAACTGCAAGAGCAAGAATGGAAGAAGCAGCTGGAGTTGGAGAAACGCTTGGAGAAACAGAGAGA CATTGTCAGGCTGAGCTCCAGAAAGAAAAGTCTCCACCTGGAACTGGAAGCAGTGAATGGAAAACATCAGCAGA TCTCAGGCAGACTACAAGATGTCCAAATCAGAAAGCAAAACACAAAAGACTGAGCTAGAAGTTTTGGATAAACAG GGTCCCTGAGAAGCAGCTATTAAACGAAAGAATTAAAAACATGCAGCTCAGTAACACCCTGATTCAGGGATCA GTTTACTTCATAAAAAGTCATCAGAAAAAGGAAGAATTATGCCAAAGACTTAAAGAACAATTAGATGCTCTTGAA AAAGAAACTGCATCTAAGCTCTCAGAAATGGATTCATTTAACAATCAGCTGAAGGAACTCAGAGAAAGCTATAA TAGAGCAAAAAAAAAAAA

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Fig. 2B

ATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAACAAAAAGAAGCCAAAAGCAGAAGGCTCCAATATGA ACAAGATAAATCTATCTTCAAAGACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAA GGAGTGAGAGGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTGTAATGTTGCTCTGA GGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCACAAATTAAGCTGTAGTATGTACCCTA AGACGCTGCTAATTGACTGCCACTTCGCAACTCAGGGGCGGCTGCATTTTAGTAATGGGTCAAATGATTCACTT TTTATGATGCTTCCAAAGGTGCCTTGGCTTCTCTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATA ATGCGGGTTTATTTCTCAGATGATGTTCATCCGTGAATGGTCCAGGGAAGGACCTTTCACCTTGACTATATGGC ATTATGTCATCACAAGCTCTGAGGCTTCTCCTTTCCATCCTGCGTGGACAGCTAAGACCTCAGTTTTCAATAGC ATCTAGAGCAGTGGGACTCAGCTGGGGTGATTTCGCCCCCCATCTCCGGGGGAATGTCTGAAGACAATTTTGTT ACCTCAATGAGGGAGTGGAGGAGGATACAGTGCTACTACCAACTAGTGGATAAAGGCCAGGGATGCTGCTCAAC CTCCTACCATGTACAGGACGTCTCCCCATTACAACTACCCAATCCGAAGTGTCAACTGTGTCAGGACTAAGAAA GGCAAATAAGCATTCTGTCTCTTTGGCTGCCTCAGCACAGAGAGCCAGAACTCTATCGGGCACCAGGATAA CATCTCTCAGTGAACAGAGTTGACAAGGCCTATGGGAAATGCCTGATGGGATTATCTTCAGCTTGTTGAGCTTC TAAGTTTCTTTCCCTTCATTCTACCCTGCAAGCCAAGTTCTGTAAGAGAAATGCCTGAGTTCTAGCTCAGGTTT TGAAGCACACACAGACTTTTGAAAGCAAGGACAATGACTGCTTGAATTGAGGCCTTGAGGAATGAAGCTTTGAA GGAAAAGAATACTTTGTTTCCAGCCCCCTTCCCACACTCTTCATGTGTTAACCACTGCCTTCCTGGACCTTGGA GCCACGGTGACTGTATTACATGTTGTTATAGAAAACTGATTTTAGAGTTCTGATCGTTCAAGAGAATGATTAAA TATACATTTCCTA

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FIG. 3

## 27/101

TTGGGGNTTTMGAGCGGCCGCCCGGGCAGGTACCGGGGTGGTCAGCGAGGAGCCATTCACACTGAACTTCACCA
TCAACAACCTGCGGTATGAGGAGAACATGCAGCACCCTGGCTCCAGGAAGTTCAACACCACGGAGAGGGTCCTT
CAGGGCCTGCTCAGGTCCCTGTTCAAGAGCACCAGTGTTGGCCCTCTGTACTCTGGCTGCAGACTTGCT
CAGACTTGAGAAACATGGGGCAGCCACTGGAGTGGACGCCATCTGCACCCTCCGCCTTGATCCCACTGGTCCTG
GACTGGACAGAGAGCGGCTATACTGGGAGCTGAGCCAGTCCTCTGGCGGNGACNCCNCTT

Fig. 7A

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 7B

TGTGGTGTTGAACTTCCTGGAGNCAGGGTGACCCATGTCCTCCCCATACTGCAGGTTGGTGATGGTGAAGTTGA GGGTGAATGGTACCAGGAGAGGGCCAGCCATAATTGTSGRGCKGSMGMSSGAGGMWGGWGTYYCWGAGGTT CYRARRTCCACTGTGGAGGTCCCAGGAGTGCTGGTGGTGGGCACAGAGSTCYGATGGGTGAAACCATTGACATA GAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTYRATGYCATTGGYCAGTTKGCTYAGCTCCCAGTACA GCCRCTCTCKGYYGMGWCCAGSGCTTTTGGGGTCAAGATGATGCAGATGCAGATGCAACACTCGTGTTTCTTTGAATA

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4.4. 254. Ovary T (inclus) GP. 364. Ovary N 4.2. 251.0 Ovary T (inclus) GP. 364. Ovary N 51.0 Sicienal muscle N 4.2. 261.0 Ovary T (inclus) GP. 364. Ovary N 52.3 264. Ovary T (inclus) GP. 364. Ovary N 52.3 264. Ovary T (inclus) GP. 324. Ovary N 6.19 948. OF 1-P (SCID) GP. 324. Ovary N 6.15 263. Ovary T (inclus) GP. 324. Large Intelettics Hole 253. Ovary T (inclus) GP. 334. Large Intelettics Hole 253. Ovary T (inclus) GP. 334. Consum N 6.10 203. Ovary T (inclus) GP. 334. Ovary N 6.10 203. Ovary T (inclus) GP. 334. Dome March N 6.10 203. Ovary T (inclus) GP. 334. Bombach N 6.10 203. Ovary T (inclus) GP. 365. Bombach N 6.10 203. Ovary T (inclus) GP. 365. Bombach N 6.10 203. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. Ovary T (inclus) GP. 365. Bombach N 6.10 478. December 1.10 478. De		162	24.5	육	IJ.	9	
44.4 429 Ovary T (iteks) 6 1 364 Ovary N 4 44.2 451 Ovary T (iteks) 6 1 510 Stelens muscle Na 4.2 43.64 Ovary T (iteks) 7 CTI 0 Stelens muscle Na 4.2 362 Ovary T CTI 0 Stelens N 4.2 364 Ovary T CTI 0 Stelens N 4.1 5 382 Ovary T CTI 0 Stelens N 4.1 5 484 Ovary T CTI 0 Stelens N 4.1 5 485 Ovary T CTI 0 Stelens N 4.1 5 486 Ovary T CTI 0 Stelens N 4.1 5 486 Ovary T CTI 0 Stelens N 4.1 5 486 Ovary T CTI 0 Stelens N 4.1 5 486 Ovary T CTI 0 Stelens N 4.1 5 486 Ovary T CTI 0 Stelens N 4.1 5 486 Ovary T CTI 0 Stelens N 4.1 5 50 Stelens N 5		2245	6.0	æ	:O	*	
4.2. 261A Ovary T (nets) CTIO Statil inicoline Na +2.3 821 Ovary T (nets) CTIO Statil inicoline Na +2.3 822 Ovary T CTIO Statil inicoline Na +2.3 822 Ovary T CTIO Kinnay Na +1.2 9483 OY 1-P (SCID) CTIO RIGHT NA +1.5 9483 OY 1-P (SCID) CTIO RIGHT NA +1.5 824 Ovary T CTIO STATE NA +1.5 825 Ovary T CTIO STATE Lange Inicitive Na +1.2 9864 Ovary T CTIO STATE Lange Inicitive Na +1.2 9864 Ovary T CTIO STATE Lange Inicitive Na +1.3 9304 Ovary T CTIO STATE Lange Inicitive Na +1.3 9304 Ovary T CTIO STATE Lange Inicitive Na +1.3 9304 Ovary T CTIO STATE Lange Inicitive Na +1.3 9304 Ovary T CTIO STATE Lange Inicitive Na +1.3 9304 Ovary T Greek Na	_	638	278	8	松	œ.	
+3.6 -8115 Ovnry T (mets) CT10 Small intestine Pt +2.3 -25.5 Ovnry T (mets) CT15 Hearth +2.3 -3.2 Ovnry T (CT15 Hearth +2.3 -3.4 Ovnry T (CT15) CT15 Hearth +1.2 -3.4 Ovnry T (CT15) CT17 Ling N +1.4 -25.4 Ovnry T (CT17 Ling N +1.4 -25.4 Ovnry T (mets) (CT17 Ling N +1.4 -25.4 Ovnry T	•	1949	30.4	8	10 17	89	
12.3 265A Ovary T CTS Hearth A 12.3 822 Ovary T CTB Kidney N 12.2 266A Ovary T CTB Kidney N 13.4 22.3 65 Ovary T (SCID) CTB Kidney N 14.5 3824 Ovary T (SCID) CTB Kidney N 14.5 2824 Ovary T (SCID) CTB Kidney N 14.5 2624 Ovary T CTB Kidney N 14.4 2624 Ovary T CTB Kidney N 14.2 2334 Ovary T CTB Kidney N 14.2 2334 Ovary T CTB Kidney N 14.2 2334 Ovary T CTB Kidney N 14.3 2334 Ovary T Kidney N 14.3 2334 Ovary T Kidney N 14.3 2334 Ovary T Kidney N 15.3 Springed N 15.3	1822	607	21.0	8	:2	\$	
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+2.1 9394 Ovary T. (SCID) 1 12 Skdn N +1.9 9483 OT 1-P (SCID) 2 5 1 9483 OT 5-P (SCID) 2 +1.5 288A Ovary T CT2 Limis N -1.5 \$23 Ovary T CT4 Joine Marrow N +1.4 282A Ovary T 2 3344 Large Intestries +1.2 293A Ovary T 2 37 Ovary N -1.0 2014 Ovary T 2 54 Ovary N -1.0 4284 Ovary T 1 metal 2 54 Ovary N		1260	143	\$	ri.	<b>9</b>	
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+1.6 382A OvaryT  +1.6 288A OvaryT  -1.5 \$25 OvaryT  +1.4 262A OvaryT  +1.2 2886A OvaryT  -1.2 393A CharyT  -1.2 393A OvaryT  -1.0 201A OvaryT  -1.0 428A Ov	2 6967	3776	41.5	2	5	2	
41,6 288A GvaryT CTT2 Ling N -1.5 \$25 OveryT CTW Bone Warrow N +1.4 262A OveryT STW Bone Warrow N +1.2 2856A OveryT STW BMC (notivated) -1.2 385A OveryT STW SS Springen N -1.0 201A OveryT (notes)	2313	100	7.9	8	5	é	
-1.5 \$25 Overy T	1687	165	10.	Ė	250	3	
+1.4 262A Ovary T 334% Large Intestrifies H. 22-886A Ovary T 340 PBMC (notivated) -1.2 -325A Ovary T 37 Ovary N 310 201A Ovary T 36 Spainsch N 1.0 -228A Ovary T. (mets) - 323A Beophenus N 323A Beophenus	848	1243		3	H	Z	
1.2 -324 Ovary T - 57 Ovary N - 1.0 2014 Ovary T - 56 Ovary N - 1.0 -224 Ovary T (mets) - 56 Spainach N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 5731 Asorbismus N - 1.0 -224 Ovary T (mets) - 1.0 -224 Ovary T (me	3 . 3171	27.4	10 10 10 10 10 10 10 10 10 10 10 10 10 1	8	oo ef	8	. •
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F1g. 11

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Sons	Name	4210182 (H7)	42110182 (HT)	42110162 (H7)	421101152 (H7)	42170182 (FHZ)	42170182 (HT)	42110182 (FFF)	42110 (82 (FH7)	421T0182 {147}	421TO 1825 (1971)	42:10182:(ET.)	42100182 (H7.)	42110182 (TEZ)	4210182 (FF)	AZITORIZ (P.E.)	42110f82 [H7]	42410182-(147)	42,110182 (FI7.)	42110182 (H7)	-42110182 (FIT.)	42,110182 (HF)	42110182 (HT)	421W182 (H7)	42110182 (H7)

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#1g. 15

f'ig. 14

## 35/101

## 11721-1

#### 11721-2

AAGGCTGGTGGTTTTTGATCCTGCTGGAGAACCTCCGCTTTCATGTGGAGGAAGAAGGGAAGGGAAAGATGC
TTCTGGGAACAAGGTTAAAGCCGAGCCAGCCAAAATAGAAGCTTTCCGAGCTTCACTTTCCAAGCTAGGGGATG
TCTATGTCAATGATGCTTTTGGCACTGCTCACAGAGCCCACAGCTCCATGGTAGGAGTCAATCTGCCACAGAAG
GCTGGTGGGTTTTTGATGAAGAAGGAGCTGAACTACTTTGCAAAGGCCTTGGAGAGCCCAGAGCGACCCTTCCT
GGCCATCCTGGGCGAGCTAAAGTTGCAGACAAGATCCAGCTCATCAATAATATGCTGGACAAAGTCAATGAGA
TGATTATTGGTGGTGGAATGGCTTTTACCTTCCTTAAGGTGCTCAACAACATGGAGATTGGCACTTCTCTGTTT
GATGAAGAGGGAGCCAAGATTGTCAAAGACCTAATGTCCAAAGCTGAGAAGAATGGTGTAAAGATTACCTTGCC
TGTTGACTTTGTCACTGCTGACAAGTTTGATGA

#### 11724-1

#### 11724-2

Fig. 15A

# 36/101 11725-32-1.2

## 11726-182

## 11727-182

Fig. 15B

# 37/101 11728.1.40.19.19

## 11728.2.40.19.19

CCCGTGGGTGCCATCCACGGAGTTGTTACCTGATCTTTGGAAGCAGGATCGCCCGTCTGCACTGCAGTGGAAGC
CCCGTGGGCAGCAGTGATGGCCATCCCCGCATGCCACGGCCTCTGGGAAGGGGCAGCAACTGGAAGTCCCTGAG
ACGGTAAAGATGCAGGAGTGGCCGGCAGAGCCAGTGGGCATCAACCTGGCAGGGGCCACCCAGATGCCTGCTCAG
TGTTGTGGGCCATTTGTCCAGAAGGGGACGGCAGCAGCTGTAGCTGGCTCCTCCGGGGTCCAGGCAGCAGCAG
CAGGGCAGAACTGACCATCTGGGCACCGCGTTCCAGCCACCAGCCCTGCTGTTAAGGCCACCCAGCTCACCAGG
GTCCACATGGTCTGCCTGCGTCCGACTCCGCGGTCCTTGGGCCCTGATGGTTCTACCTGCTGTGAGCTGCCCAG
TGGGAAGTATGGCTGCCCAATGCCCAACGCCACCTGCTCCCGATCACCTGCACTGCCCCAAGACACT
GTGTGTGACCTGATCCAGAGTAAGTGCCTCTCCAAGGAGAACG

## 11730-1

## 11730-2

Fig. 15C

## 38/101

# 11732.1contig

## 11732.2contig

### 11735-1-2

#### 11740.2.contia

Fig. 15D

## 39/101

## 11765.2&64.2.contig

## 11767.2.contig

CCCGGAGCCAACGAGCGGAAAATGGCAGACAATTTTTCGCTCCATGATGCGTTATCTGGGTCTGGAAACC
CAAACCCTCAAGGATGGCCTGGCGCATGGGGGAACCAGCCTGCTGGGGCAGGGGGCTACCCAGGGGCTTCCTAT
CCTGGGGCCTACCCCGGGCAGCCCCCCAGGGGCTTATCCTGGACAGCCACCTCCAGGCGCCTACCCTGGAGC
ACCTGGAGCTTATCCCGGAGCACCTGCACCTGGAGTCTACCCAGGGCCCCCCAGCGGCCCCTGGGGCCTACCCAT
CTTCTGGACAGCCAAGTGCCACCGGAGCCTACCCTGCCACTGGCCCCCTATGGCGCCCCTGCTGGGCCACTGATT
GTGCCTTATAACCTGCCTTTGCCTGGGGGAGTGGTGCCTCGCATGCTGATAACAATTCTGGGCACGGTGAAGCC
CAATGCAAACAGAATTGCTTTAGATTTCCAAAGAGGGAATGATGTTGCCTTCCACTTTAACCCACGCTTCAATG
AGAACAACAGGAGAGTCATTGGTTGCAATACAAAGCTGGATAA

## 11768-1&2

GGGAATGCAACAACTTTATTGAAAGGAAAGTGCAATGAAATTTGTTGAAACCTTAAAAGGGGAAACTTAGACAC CCCCCCTCRAGCGMAGKACCARGTGCARAGGTGCAATGACATCTTTCTGGATGTTGTAGTCAGACAGGGTRCGWCCATC TTCCAGCTGTTTYCCRGCAAAGATCAACCTCTGCTGATCAGGAGGGRATGCCTTCCTTATCTTGGATCTTTGCCT TGACATTCTCGATGGTGTCACTGGGCTCCACCTCGAGGGTGATGGTCTTACCAGTCAGGGTCTTCACGAAGATY TGCATCCCACCTCTGAGACGGAGCACCAGGTGCAGGGTRGACTCTTTCTGGATGTTGTAGTCAGACAGGGTGCG YCCATCTTCCAGCTGCTTTCCC3aGCAAAGATCAACCTCTGCTGGTCAGGAGGRATGCCTTCCTTGTCYTGGATC TTTGCYTTGACRTTCTCAATGGTGTCACTCGGCTCCACTTCGAGAGTGATGGTCTTACCAGTCAGGGTCTTCAC GAAGATCTGCATCCCACCTCTAAGACGGAGCACCAGGTGCAGGGTGGACTCTTTCTGGATGGTTTTCAGACACAGGTGCGTCCACCTCTCCAGCTGCTTCCCAGCAAAGATCAACCT

# 40/101

## 11768-1&2-11735-1&2

## 11769.1.contig

## 11769.2.contig

## 11770.1.contig

Fig. 15F

## 41/101

## 11770.2.contig

## 11773.1.contig

## 11778.1.contig

#### 11778-2830-2

Fig. 15G

## 42/101

## 11782.1.contig

ATCTACGTCATCAATCAGGCTGGAGACACCATGTTCAATCGAGCTAAGCTGCTCAATATTGGCTTTCAAGAGGC
CTTGAAGGACTATGATTACAACTGCTTTGTGTTCAGTGATGTGGACCTCATTCCGATGGACGACCGTAATGCCT
ACAGGTGTTTTTCGCAGCCACGGCACATTTCTGTTGCAATGGACAAGTTCGGGTTTAGCCTGCCATATGTTCAG
TATTTTGGAGGTGTCTCTGCTCTCAGTAAACAACAGTTTCTTGCCATCAATGGATTCCCTAATAATTATTGGGG
TTGGGGAGGAGAAGATGACGACATTTTTAACAGATTAGTTCATAAAGGCATGTCTATATCACGTCCAAATGCTG
TAGTAGGGAGGTGTCGAATGATCCGGCATTCAAGAGACAAGAAAAATGAGCCCAATCCTCAGAGGTTTGACCGG
ATCGCACATACAAAGGAAACGATGCGCTTCGATGGTTTGAACTCACTTACCTACAAGGTGTTGGATGTCAGAGA
TACCCGTTATATACCCAAATCAC

## 11782.2.contig

#### 11783-1 & 2

#### 11786.1.contia

GCTCTTCACACTTTTATTGTTAATTCTCTTCACATGGCAGATACAGAGCTGTCGTCTTGAAGACCACCACTGAC CAGGAAATGCCACTTTTACAAAATCATCCCCCCTTTTCATGATTGGAACAGTTTTCCTGACCGTCTGGGAGCGT TGAAGGGTGACCAGCACATTTGCACAAAAAAGGAGTGACCCCAAGGCCTCAACCACACTTCCCAGAGCTC ACCATGGGCTGACACACATTTGCAGGGTTTGGGGTTCGTGAGGCTTTCCTTGCTGCTGCGGTGGGGAGGCCCTCA AGAACTGAGAGGCCCGGGGTATGCTTCATGAGTTTAACATTTACGGGACAAAAGCGCATCATTATGAAAATTTAA AGCAAACAGCGCTTTTTTAGCTGGGTGGGAAACAGGAAACAACAGCGTTTTTTAGCTGGGAAACAACAGCGTTTTTTAGCTGGAAACAACAGGTTTTTTAGCTGGGAAACAACAGGTTTTTTAGCTCCCCATGAAACC

# Fig. 15H

## 43/101

## 11786.2.contig

CAAGCGCTTGGCGTTTGGACCCAGTTCAGTGAGGTTCTTGGGTTTTTGTGCCTTTGGGGATTTTGGTTTGACCCA GGGGTCAGCCTTAGGAAGGTCTTCAGGAGGAGGCCGAGTTCCCCTTCAGTACCACCCCTCTCCCCACTTTCC CTCTCCCGGCAACATCTCTGGGAATCAACAGCATATTGACACGTTGGAGCCGAGCCTGAACATGCCCCTCGGCC CCAGCACATGGAAAACCCCCTTCCTTGCCTAAGGTGTCTGAGTTTCTGGCTCTTGAGGCATTTCCAGACTTGAA ATTCTCATCAGTCCATTGCTCTTTGAGTCTTTTGCAGAGAAACCTCAGATCAGGTGCACCTGGGAGAAAGACTTTGT CCCCACTTACAGATCTATCTCCTCCCTTGGGAAGGGCAGGGAATGGGGACGGTGTATGGAGGGGAAGGGATCTC CTGCGCCCTTCATTGCCACACTTGGTGGGACCATGAACATCTTTAGTGTCTGAGCTTCTCAAATTACTGCAATA GGA

## 13691.182

## 13692.182

#### 13693.2

Fig. 15I

# 44/101 13696.1-13744.1

## 13700.1

CAAGGATATATGTTGAGGGTACRGRGTGACACTGAACAGATCACAAAGCACGAGAAACATTAGTTCTCTCCCT
CCCCAGCGTCTCCTTCGTCTCCCTGGTTTTCCGATGTCCACAGAGTGAGATTGTCCCTAAGTAACTGCATGATC
AGAGTGCTGKCTTTATAAGACTCTTCATTCAGCGTATCCAATTCAGCAATTGCTTCATCAAATGCCGTTTTTGC
CAGGCTACAGGCCTTTTCAGGAGAGTTTAGAATCTCATAGTAAAAGACTGAGAAATTTAGTGCCAGACCAAGAC
GAATTGGGTGTGAGGCTGCATTNCTTTCTTACTAATTTCAAATGCTTCCTGGTAAGCCTGCTGGGAGTTCGAC
ACAAGTGGTTTTGTTTGTTTGCTCCAGATGCCACTTCAGAAAGATACCTAAAATAATCTCCTTTCATTTTCAAAGT
AGAACAC

## 13700.2

#### 13701.1

## 45/101

## 13701.2

#### 13702.2

AGCTGGCGCTAGGGCTCGGTTGTGAAATACAGCGTRGTCAGCCCTTGCGCTCAGTGTAGAAACCCACGCCTGTA AGGTCGGTCTTCGTCCATCTGCTTTTTTCTGAAATACACTAAGAGCAGCCACAAAACTGTAACCTCAAGGAAAC CATAAAGCTTGGAGTGCCTTAATTTTTAACCAGTTTCCAATAAAACGGTTTACTACCT

## 13704.2-13740.2

GGAGATGAAGATGAGGAAGCTGAGTCAGCTACGGGCARGCGGGCAGCTGAAGATGATGAGGATGACGATGTCGA TACCAAGAAGCAGAAGACCGACGACGATGACTAGACAGCAAAAAAGGAAAAGTTAAA

#### 13706.1

GATGAAAATTAAATTAAATTAATCAAAAGGCACTACGATACCACCTAAAACCTACTGCCTCAGTGGCAGTA KGCTAAKGAAGATCAAGCTACAGSACATYATCTAATATGAATGTTAGCAATTACATAKCARGAAGCATGTTTGC TTTCCAGAAGACTATGGNACAATGGTCATTWGGGCCCAAGAGGATATTTTGGCCNGGAAAGGATCAAGATAGATN AANGTAAAG

## 13706.2

Fig. 15K

## 46/101

### 13707.3

## 13710.2

## 13710-1

TGAGATTTATTGCATTTCATGCAGCTTGAAGTCCATGCAAAGGRGACTAGCACAGTTTTTAATGCATTTAAAAA
ATAAAAGGGAGGTGGGCAGCAAACACACAAAGTCCTAGTTTCCTGGGTCCCTGGGAGAAAAGAGTGTGGCAATG
AATCCACCCACTCTCCACAGGGAATAAATCTGTCTCTTAAATGCAAAGAATGTTTCCATGGCCTCTGGATGCAA
ATACACAGAGCTCTGGGGTCAGAGCAAGGGATGGGGAGAGACCACGAGTGAAAAAGCAGCTACACACATTCAC
CTAATTCCATCTGAGGGCAAGAACAACGTGGCAAGTCTTGGGGGTAGCAGCTGTT

## 13711.1

## 47/101

#### 13711.2

## 13713.1&2

TCACTTTATTTTCTTGTATAAAAACCCTATGTTGTAGCCACAGCTGGAGCCTGAGTCCGCTGCACGGAGACTC
TGGTGTGGGTCTTGACGAGGTGGTCAGTGAACTCCTGATAGGGAGACTTTGGTGAATACAGTCTCCTTCCAGAGG
TCGGGGGTCAGGTAGCTGTAGGTCTTAGAAATGGCATCAAAGGTTGGCCTTGGCGAAGTTGCCCAGGGTGGCAGT
GCAGCCCCGGGCTGAGGTGTAGCAGTCATCGATACCAGCCATCATGAG

## 13715.4

## 13717.1&2

TGAATGGGGAGGAGCTGACCCAGGAAATGGAGCTTGNGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAG
TGGGCATCTGTGGTGGTGCCTCTTGGGAAGGAGCAGAAGTACACATGCCATGTGGAACATGAGGGGCTGCCTGA
GCCCCTCACCCTGAGATGGGGCAAGGAGGAGCCTCCTTCATCCACCAAGACTAACACAGTAATCATTGCTGTTC
CGGTTGTCCTTGGAGCTGTGGTCATCCTTGGAGCTGTGATGGCTTTTTGTGATGAAGAGGAGGAGAAACACAGGT
GGAAAAGGAGGGGACTATGCTCTGGCTCCAGGCTCCCAGAGCTCTGATATGTCTCTCCCAGATTGTAAAGTGTG
AAGACAGCTGCCTGGTGTGGACTTGGTGACAGACAATGTCTTCACACATCTCCTGTGACATCCAGAGACCTCAG
TTCTCTTTAGTCAAGTGTCTGATGTTCCCTGTGAGTCTGCGGGCTCAAAGTGAAGAACCTGTGGAGCCCAGTCCA
CCCCTGCACACCAGGACCCTATCCCTGCACTGCCCTGTGTTCCCTTCCACAGCCAACCTTGCTGCTCCAGCCAA
ACATTGGTGGACATCTGCAGCCTGTCAGCTCCATGCTACCCTGACCTTCCACAGGTCCTGAGAAT
AATAATTTGAATGTGGGTGGCTGGAGAGAGATGGCTCAGCGCTGACTTCTCCACAGGTCCTGAGGTTCAAATCC
CAGCAACCACATGGTGGCTCACAACCATCTGTAATGGGATCTAATACCCTCTTCTGCAGTGTCTGAAGACASCT
ACAGTGTACTTACATATAATAATAAATAAA

Fig. 15M

## 48/101

## 13719.1&2

## 13721.1

#### 13721.2

## 13723.1

CATGGGTTTCACCAGGTTGGCCAGGCTGCTCTTGAACTSCTGACCTCAGGTGATCCACCCGCCTCGGCCTCCCA
AAGTGCTGGGATTACAGGCGTGAGCCACCACGCCCGGCCCCCAAAGCTGTTTCTTTTTGTCTTTAGCGTAAAGCT
CTCCTGCCATGCAGTATCTACATAACTGACGTGACTGCAGCAAGCTCAGTCACTCCGTGGTCTTTTTCTCTTT
CCAGTTCTTCTCTCTCTCTCAAGTTCTGCCTCAGTGAAAGCTGCAGGTCCCCAGTTAAGTGATCAGGTGAGGG
TTCTTTGAACCTGGTTCTATCAGTCGAATTAATCCTTCATGATGG

Fig. 15N

## 49/101

## 13723.2

## 13725.1

## 13725.2

#### 13726.1&2

## 50/101

#### 13727.1

### 13727.2

ACCTAGACAGAAGGTGGGTGAGGGAGGACTGGTAGGAGGCTGAGGCAATTCCTTGGTAGTTTGTCCTGAAACCC
TACTGGAGAAGTCAGCATGAGGCACCTACTGAGAGAAGTGCCCAGAAACTGCTGACTGCATCTGTTAAGAGTTA
ACAGTAAAGAGGTAGAAGTGTTTTCTGAATCAGAGTGGAAGCGTCTCAAGGGTCCCACAGTGGAGGTCCCTGA
GCTACCTCCCTTCCGTGAGTGGGAAGAGTGAAGCCCATGAAGAACTGAGATGAAGCAAGGATGGGGTTCCTGGG
CTCCAGGCAAGGGCTGTGCTCTCTGCAGCAGGAGGCCCCACGAGTCAGAAGAAAAGAACTAATCATTTGTTGCA
AGAAACCTTGCCCGGATACTAGCGGAAAACTGGAGGCGGNGGTGGGGGCACAGGAAAAGTGGAAGTGATTTGATG
GAGAGCAGAGAAGCCTATGCACAGTGGCCGAGTCCACTTGTAAAGTG

### 13728.182

#### 13731.1&2

# 51/101

### 13734.182

### 13736.2

## 13744.2-13696.2

### 13746.1&2-13720.1&2

### 52/101

### 14347.1

CAGATTTTTATTTGCAGTCGTCACTGGGGCCGTTTCTTGCTGCTTATTTGTCTGCTAGCCTGCTCTTCCAGCTG
CATGGCCAGGCGCAAGGCCTTGATGACATCTCGCAGGGCTGAGAAATGCTTGGCTTGCTGGGCCAGAGCAGATT
CCGCTTTGTTCACAAAGGTCTCCAGGTCATAGTCTGGCTGCTCGGTCATCTCAGAGAGCCCAGTCTGGT
CCTTGCTGTATGATCTCCTTGAGCTCTTCCATAGCCTTCTCCTCCAGCTCCCTGATCTGAGTCATGGCTTCGTT
AAAGCTGGACATCTGGGAAGACAGTTCCTCCTCTTCCTTGGATAAATTGCCTGGAATCAGCGCCCCGTTAGAGC
AGGCTTCCATCTCTTCTGTTTCCATTTGAATCAACTGCTCTCCACTGGGCCCCACTGTGGGGGGCTCAGCTCCTTG
ACCCTGCTGCATATCTTAAGGGTGTTTAAAGGATATTCACAGGAGCTTATGCCTGGT

### 14347.2

### 14348.2&14350.1&2

### 14349.1&2

TTCGTGAAGACCCTGACTGGTAAGACCATCACTCTCGAAGTGGAGCCCGAGTGACACCATTGAGAATGTCAAGG CAAAGATCCAAGACAAGGAAGGCATCCCTCCTGACCAGCAKAGGTTGATCTTTGCTGGGAAACAGCTGGAAGAT GGACGCACCCTGTCTGACTACAACATCCAGAAAGAGTCCACCCTGCACCTGGTGCTCCGTCTCAGAGGTGGGAT GCAAATCTTCGTGAAGACCCTGACTGGTAAGACCATCACCCTCGAGGTGGAGCCCAGTGACACCATCGAGAATG TCAAGGCAAAGATCCAAGATAAGGAAGGCATCCCTCCTGATCAGCAGAGGTTGATCTTTGCTGGGAAACAGCTG GAAGATGGACGCACCCTGTCTGACTACAACATCCAGAAAGAGTCCACTTTCCACTTGCACTTGCGCTTTGAGGGG GGGTGTCTAAGTTTCCCCTTTTAAGGTTTCAACAAATTTCATTGCACTTTCCTTTCAATAAAGTTGTTGCATTC

Fig. 15R

### 53/101

### 14352.182

#### 14353.1

#### 14353.2

#### 17182.182

Fig. 15S

# 54/101

### 17183.2

GGTTCACAGCACTGCTGCTTGTTGTCCGGCCAGGAATTCCAGGCTCACAAGGCTATCTTAGCAGCTCGTTC
TCCGGTTTTTAGTGCCATGTTTGAACATGAAATGGAGGAGAGCAAAAAGAATCGAGTTGAAATCAATGATGTGG
AGCCTGAAGTTTTTAAGGAAATGATGTGCTTCATTTACACGGGGAAGGCTCCAAACCTCGACAAAATGGCTGAT
GATTTGCTGGCAGCTGCTGACAAGTATGCCCTGGAGCGCTTAAAGGTCATGTGTGAGGATGCCCTCTGCAGTAA
CCTGTCCGTGGAGAAACGCTGCAGAAATTCTCATCCTGGCCGACCTCCACAGTGCAGATCAGTTGAAAACTCAGG
CAGTGGATTTCATCAACTATCATGCTTCGGATGTCTTGGAGACCTCTTGGG

### 17186,182

#### 17187.182

#### 17191.1889.1

# 55/101 17192.182

### 17193

### 56/101

#### 16443.1.edit

### 16443.2.edit

#### 16444.2.edit.

#### 16445.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCCGGGCGGCCGCTCGA

Fig. 15V

### 57/101

### 16445.2.edit

### 16446.1.edit

TCGAGCGCCCCGGGCAGGTCCTCCTCAGAGCGGTAGCTGTTCTTATTGCCCCGGCAGCCTCCATAGATNAA GTTATTGCANGAGTTCCTCTCCACGTCAAAGTACCAGCGTGGGAAGGATGCACGGCAAGGCCCAGTGACTGCGT TGGCGGTGCAGTATTCTTCATAGTTGAACATATCGCTGGAGTGGACTTCAGAATCCTGCCTTCTGGGAGCACTT GGGACAGAGGAATCCGCTGCATTCCTGCTGGTGGACCTCGGCCGCCGACCACGCT

### 16446.2.edit

AGCGTGGTCGCGGCCGAGGTCCACCAGCAGGAATGCAGCGGATTCCTCTGTCCCAAGTGCTCCCAGAAGGCAGG ATTCTGAAGACCACTCCAGCGATATGTTCAACTATGAAGAATACTGCACCGCCAACGCAGTCACTGGGCCTTGC CGTGCATCCTTCCCACGCTGGTACTTTGACGTGGAGAGGAACTCCTGCAATAACTTCATCTATGGAGGCTGCCG GGGCAATAAGAACAGCTACCGCTCTGAGGAGGACCTGCCCGGGCGGCCGCTCGA

### 16447.1.edit

Fig. 15W

### 58/101

### 16447.2.edit

### 16449.1.edit

### 16450.1.edit

### 16450.2.edit

Fig. 15X

### 59/101

### 16451.1.edit

### 16451.2.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGNTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGTACCTCTGGTGAGGACCTCGGCCGCACCACG
CT

#### 16452.1.edit

### 16452.2.edit

Fig. 15Y

### 60/101

### 16453.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCCGAACTGCCAGTGTACAGGGAAGATGTACATGTTATAGNTCTTCTCGAA GTCCCGGGCCAGCAGCTCCACGGGGTGGTCTCCTCCCCCCCAGGCGCTTCTCATTCTCATGGATCTTCTTCACCC GCAGCTTCTGCTTCTCAGTCAGAAGGTTGTTGTCCTCATCCCTCATACAGGGTGACCAGGACGTTCTTGAGC CAGTCCCGCATGCGCAGGGGGAATTCGGTCAGCTCAGAGTCCAGGCAAGGGGGGATGTATTTGCAAGGCCCGAT GTAGTCCAAGTGGAGCTTGTGGCCCTTCTTGGTGCCCTCCAAGGTGCACTTTGTGGCAAAGAAGTGGCAGGAAG AGTCGAAGGTCTTGTTGTCATTGCTGCACACCTTCTCAAACTCGCCAATGGGGGCTGGGCAGACCTGCCCGGGC GGCCGCTCGA

### 16453.2.edit

#### 16454.1.edit.

AGCGTGGNTGCGGACGCCCACAAAGCCATTGTATGTAGTTTTANTTCAGCTGCAAANAATACCNCCAGCATCCCACCTTACTAACCAGCATATGCAGACA

#### 16454.2.edit

TCGAGCGGTCGCCCGGGCAGGTCTGGGCGGATAGCACCCGGGCATATTTTGGAATGGATGAGGTCTGGCACCCTG
AGCAGCCCAGCGAGGACTTGGTCTTAGTTGAGCAATTTGGCTAGGAGGATAGTATGCAGCACGGTTCTGAGTCT
GTGGGATAGCTGCCATGAAGNAACCTGAAGGAGGCGCTGGCTGGTANGGGTTGATTACAGGGCTGGGAACAGCT
CGTACACTTGCCATTCTCTGCATATACTGGNTAGTGAGGCGAGCCTGGCGCTCTTCTTTGCGCTGAGCTAAAGC
TACATACAATGGCTTTGNGGACCTCGGCCGCGACCACGCTT

Fig. 15Z

### 61/101

### 16455.1.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGACACCATCTAGATGAATCACATCTGAAATGACCACTTCCCAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGC CTCTGCTGGTCTTTCAAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCGACCA CGCT

### 16455.2.edit

### 16456.1.edit

#### 16456.2.edit

Fig. 15AA

### 62/101

### 16459.1.edit

### 16459.2.edit

### 16460.1.edit

TCGAGCGGCCCCGGGCAGGTCCATTTTCTCCCTGACGGNCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCNTCCCCGAACCTTATGC
CTCTGCTGGGGCTTTCAGNGCCTCCACTATGATGNTGTAGGGGGGCACCTCTGGNGANGACCTCGGCCGCGACCA
CGCT

#### 16460.2.edit

Fig. 15BB

**SUBSTITUTE SHEET (RULE 26)** 

### 63/101

### 16461.1.edit

### 16461.2.edit

### 16463.1.edit

AGCGTGGNNGCGGCCGAGGTATAAATATCCAGNCCATATCCTCCCTCCACACGCTGANAGATGAAGCTGTNCAA AGATCTCAGGGTGGANAAAACCAT

#### 16463.2.edit

Fig. 15CC

### 64/101

### 16464.1.edit

CGAGCGGCCGACCGGCCAGGTNCAGACTCCAATCCANANAACCATCAAGCCAGATGTCAGAAGCTACACCATCA CAGGTTTACAACCAGGCACTGACTACAAGANCTACCTGCACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTTGCT GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGTACATCATCNAGTATGANAAGCCTGGGCCTCCTCCCAG AGAAGNGGTCCCTCGGCCCCCGCCTGNTGTCCCANAGGNTACTATTACTGNGCCNGCAACCGGCAACCGATATC NATTTTGNCATTGGCCTTCAACAATAATTA

### 16464.2.edit

AGCGTGGTTCGCGGCCGANGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTTC
TTCATCAGNGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTTG
TCTGAGAGAGAGACTTCTTGNCCTGTCTTTTTCCTTCCAATCAGGGGCTCGCTCTTCTGATTATTCTTCAGGGCA
ATGACATAAATTGTATATTCGGGTCCCGGNTCCAGGCCAGTAATAGTANCCTCTGTGACACCAGGGCGGNGCCG
AGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGAACCGGTAATCCTGGCACGTGGCG
GCTGCCATGATACCAGCAAGGAATTGGGGTGTGGCCAGGAAACGCAGGTTGGATGGNGCATCAATGGCAGT
GGAGGCCGTCGATGACCACAGGGGGGAGCTCCGACATTGTCATTCAAGGTG

### 16465.1.edit

AGCGTGGNCGCGGCCGAGGTGCAGCGCGGGCTGTGCCACCTTCTGCTCTCTGCCCAACGATAAGGAGGGTNCCTGCCCCAGGAGAACATTAACTNTCCCCAGCTCGGCCTCTGCCGG

#### 16465.2.edit

TCGAGCGCCCCCGGGCAGGTTTTTTTTTGCTGAAAGTGGNTACTTTATTGGNTGGGAAAGGGAGAAGCTGTGG
TCAGCCCAAGAGGGAATACAGAGNCCCGAAAAAGGGGAGGGCAGGTGGGCTGGAACCAGACCACAGCCAGGCCAGGCA
GAAACTTTCTCTCCTCACTGCTCAGCCTGGTGGTGGCTGGAGCTCANAAATTGGGAGTGACACAGGACACCTTC
CCACAGCCATTGCGGCGGCATTTCATCTGGCCAGGACACTGGCTGTCCACCTGGCACTGGTCCCGACAGAAGCC
CGAGCTGGGGAAAGTTAATGTTCACCTGGGGGCAGGAACCCTCCTTATCATTGNGCAGAGAGCAGAAGGTGGCA
CAGCCCGCGCTGCACCTCGGCCGCACCACGCT

## 16466.2.edit

TCGAGCGGCCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGNCTTCTCCTTGGGGGGNCACCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGCG
TCCACTGGGCGCTCAGGCT

# 16467.2.edit

TCGAGCGGTTCGCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCCACGTGCCAGGA
TTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGCCGGTCCCTCGGCCCCTGGT
GTCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGNCCTGAAGAATAA
TCANNAANAGCGANCCCCTGATTGGAAGGA

# Fig. 15DD

**SUBSTITUTE SHEET (RULE 26)** 

# 65/101 01 16469.edit

## 02 16469.edit

# 03\_16470.edit

# 04\_16470.edit

TCGAGCGCCCCGGGCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTTCTCATCAGTGCCAACAGGATGACATGAAATGATGTCCTAGAAGTGTCCTGGAATGGGCCCATGAGATGGTTGTCTGAGAGAGGAGAGAGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCCTATGCCTTATGGGGGTGGCCGTTGTGGGCGGTGTGCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAGTGCCAGGAAGCTGAATACCATTTCACCTCGGCCGCGACCACGCTA

## 05 16471.edit

TCGAGCGCCCCCGGGCAGGTCTCCCTTCTTGCGGCCCAGGGCAGCGCATAGTGGGACTCGTACCACTGTCG
GTACGGTGTGCTGTCGATGAGCACGATGCAATTCTTCACCAGGGTCTTGGTACGAACCAGCTCGTTATTAGATG
CATTGTAGACAACATCGATGATCCTTGTTTTACGAGTACAACACTCTGAGCCCCAGGAGAAATTCCCCACGTCC
AACCTCAGGGCACGGTATTTCTTGTTACCTCCCCGCACACGGACTGTGTGGATGCGGCGGGGGCCAAGCTGACT
CCTGAGGAAGAAGAAGAATTTTAAACAAAAAAACGATCTAAAAAAATTCAGAAGAAATATGATGAAAGGAAAAAAAGAA
TGCCAAAATCAGCAGTCTCCTGGAGGAGCAGTTCCAGCAGGGCAAGCTTCTTGCGTGCATCGCTTCAAGGCCGG
GACAGTGTGACCGAGCAGATGGCTATGTGCTAGAGGGCAAAAGAAGTGGAGTTCTATCTTAAGAAAATCAGGGCC
CAGAATGGTGNGTCTTCAACTAATCCAAAGGGGAGTTTCAGACCAGTGCAATCAGCAAAAACATTGATACTGNT
GGCCAAATTTATTGGTGCAGGGCTTGCACANTANGANNGGCTGGGTCTTGGGGCTTGGATTGGNACAAGCTTTTG
GCAGCCTTTTCTTTGGTTTTTGCCAAAAAACCTTTTGNTGAAGANGANACCTNGGGCGGACCCCTTAACCGATTCC
ACNCCNGGNGGCGTTCTANGGNCCCNCTTG

# Fig. 15EE

# 66/101 06 16471.edit

AGCGTGGTCGCGGCCGAGGTCTGCTGCTTCAGCGAAGGGTTTCTGGCATAACCAATGATAAGGCTGCCAAAGAC
TGTTCCAATACCAGCACCAGAACCAGCCACTCCTACTGTTGCAGCACCTGCACCAATAAATTTGGCAGCAGTAT
CAATGTCTCTGCTGATTGCACTGGTCTGAAACTCCCTTTGGATTAGCTGAGACACACCATTCTGGGCCCTGATT
TTCCTAAGATAGAACTCCAACTCTTTGCCCTCTAGCACATAGCCATCTGCTCGGTCACACTGTCCCGGCCTTGA
AGCGATGCACGCAAGAAGCTTGCCCTGCTGGAACTGCTCCTCCAGGAGACTGCTGATTTTTGGCATTCTTTTTCC
TTTCATCATATTTCTTCTGAATTTTTTTTAGATCGTTTTTTTGTTTAAAATCTCTTCTTCCTCAGGAGTCAGCTTG
GCCCCCGCCGCATCCACACAGTCCGTGTGCGGGGAGGTAACAAGAAATACCGTGCCCTGAGGTTGGACGTGGGG
AATTTCTCCTGGGGCTCAGAGTGGTGTACTCGTAAAACAAGGATCATCGATGGTGNCTACAATGCATCTAATAA
CGAGCTGGGTCGGACCCAAAGAACCTGGNGAANAAATGGATCGNCTCATCGACAGGACACCGTACCCGACAGGG
GNACGANTCCCACTATGCGCTTGCCCCTGGGCCGCAANAAAGGAAAAACTGCCCGGGCGGCCNTCGAAAGCCCAA
TTNTGGAAAAAAATCCATCACACTGGGNGGCCNGTCGAGGCATGCATNTANAGGGGCCCCATTCCCCCTNANN

# 07\_16472.edit

TCGAGCGCCCCGGCCAGGTCCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAG ACTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAA GGACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCG ACCCTGCCGATGTGGACCTCGGCCGCGACCACGCT

# 08\_16472.edit

AGCGTGGTCGCCGACGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGACCTGCCCGGGCGGCCGCTCGA

### 09 16473.edit

Fig. 15FF

# 67/101

# 11\_16474.edit

## 12 16474.edit

# 13\_16475.edit

TCGAGCGCCCCCGGGCAGGTCTGGTCCAGGATAGCCTGCGAGTCCTCCTACTGCTACTCCAGACTTGACATC
ATATGAATCATACTGGGGAGAATAGTTCTGAGGACCAGTAGGGCATGATTCACAGATTCCAGGGGGGCCAGGAG
AACCAGGGGACCCTGGTTGTCCTGGAATACCAGGGTCACCATTTCTCCCAGGAATACCAGGAGGGCCTGGATCT
CCCTTGGGGCCTTGAGGTCCTTGACCATTAGGAGGGCGAGTAGGAGCAGTTGGAGGCTGTGGGCAAACTGCACA
ACATTCTCCAAATGGAATTTCTGGGTTGGGGCAGTCTAATTCTTGATCCGTCACAATATTATGTCATCGCAGAGA
ACGGATCCTGAGTCACAGACACATATTTTGGCATGGTTCTGGCTTCCAGACATCTCTATCCGNCATAGGACTGAC
CAAGATGGGAACATCCTCCTTCAACAAGCTTNCTGTTGTGCCAAAAATAATAGTGGGATGAAGCAGACCGAGAA
GTANCCAGCTCCCCTTTTTTGCACAAAGCNTCATCATGTCTAAATATCAGACATGAGACTTCTTTGGGCAAAAAAA
GGAGAAAAAGAAAAAGCAGTTCAAAGTANCCNCCATCAAGTTGGTTCCTTTGCCCNTTCAGCACCCGGGCCCCGT
TATAAAACACCCTNGGGCCGGACCCCCCTT

# Fig. 15GG

# 68/101 14 16475.edit

# 15\_16476.edit

# 16\_16476.edit

Fig. 15HH

# 17\_16477.edit

# 18\_16477.edit

AGCGTGGTTNGCGGCCGAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCTCACCAGGAAGCCCACGGGCTCCTGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCTTCAATCCATNCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACCGAGCACCCTGTGGTCCAACAACTCCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTTGCCAGGAGGACCAGCAGCAGCACCAGCCTTACCAACCTGCCCGGGCCGCCCCCGA

## 21 16479.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCACCACG
CT

## 22 16479.edit

# Fig. 15II

## 24\_16480.edit

TCGAGCGNNCGCCCGGGCAGGTCCAGTAGTGCCTTCGGGACTGGGTTCACCCCCAGGTCTGCGGCAGTTGTCAC
AGCGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCT
CCTACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTT
CCCAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTT
TACTTCCTCCTTCTCTACTGGAGCTTTCGTACCTTCCACTTCTGCTGTTGGTAAAATGGTGGATCTTCTATCAA
TTTCATTGACAGTACCCCACTTCTCCCAAACATCCAGGGAAATAGTGATTTCAGAGCGATTAGGAGAACCAAATT
ATGGGGCAGAAATAAGGGGCTTTTCCACAGGTTTTCCTTTGGAGGAAGATTTCAGTGGTGACTTTAAAAGAATA
CTCAACAGTGTCTTCATCCCCATAGCAAAAGAAGAACACTTCAGTTTACANNAAGNCACATANTCTGACTCANAA
AGGACCCAAGTAGCNCCATGGNCAGCACTTTNAGCCTTTCCCCTGGGGAAAANNTTACNTTCTTAAANCCTNGG
CCNNGACCCCCTTAAGNCCAAATTNTGGAAAANTTCCNTNCNNCTGGGGGGGCNGTTCNACATGCNTTTNAAGGG
CCCAATTNCCCCNT

# 25\_16481.edit

## 26 16481.edit

# 27\_16482.edit

TCGAGCGCCCCGGGCAGGTTGAATGGCTCCTCGCTGACCACCCCGGTGCTGGTGGTGGTACAGAGCTCCG ATGGGTGAAACCATTGACATAGAGACTGTCCCTGTCCAGGGTGTAGGGGCCCAGCTCAGTGATGCCGTGGGTCA GCTGGCTCAGCTTCCAGTACAGCCGCTCTCTGTCCAGTCCAGGGCTTTTGGGGTCAGGACGATGGGTGCAGACA GCATCCACTCTGGTGGCTGCCCCCATCCTTCTCAGGCCTGAGCAAGGTCAGTCTGCAACCAGAGTACAGAGAGCT GACACTGGTGTTCTTGAACAAGGGCATAAGCAGACCCTGAAGGACACCTCGGCCGCGACCACGCT

# Fig. 15JJ

# 71/101 28 16482.edit

## 29 16483.edit

# 31 16484.edit

# 37\_16487.edit

AGCGTGGTCGCGGCCGAGGTCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT CCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCCAAGGTGGACAAGAGA GTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTC AGTCTTCCTCTTCCCCCGCATCCCCCTTCCAAACCTGCCCGGGCGGCCGCTCG

Fig. 15KK

# 72/101 38 16487.edit

CGAGCGGCCGCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGACTGACGGTCCCCCCAGGAGTTCA GGTGCTGGGCACGGTGGGCATGTTGTGAGTTTTGTCACAAGATTTGGGCTCAACTCTCTTGTCCACCTTGGTGTT GCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGTGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTGC TGAGGGAGTAGAGTCCTGAGGACTGTAGGACAGACCTCGGCCGCGACCACGCT

39 16488.edit

NGGNNGGTCCGGNCNGNCAGGACCACTCNTCTTCGAAATA

### 41 16489.edit

AGCGTGGTCGCGGCCGAGGTCCTCACTTGCCTCCTGCAAAGCACCGATAGCTGCGCTCTGGAAGCGCAGATCTG
TTTTAAAGTCCTGAGCAATTTCTCGCACCAGACGCTGGAAGGGAAGTTTGCGAATCAGAAGTTCAGTGGACTTC
TGATAACGTCTAATTTCACGGAGCGCCACAGTACCAGGACCTGCCCGGGCCGCCGCTCGA

# 42\_16489.edit

### 45 16491.edit

TCGAGCGCCCCCGGGCAGGTCCACATCGGCAGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

Fig. 15LL

**SUBSTITUTE SHEET (RULE 26)** 

# 73/101 46 16491.edit

# 47 16492.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGACAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATTGCACCACAGGAC
CAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAGTAT
GTGGTTAAGTGTCTATGCTCAGAATCCAAGCGGAGAGAAGTCAGCCTCTGGTTCAGACTGNAAGTAACCAACAT
TGATCGCCTAAAGGACTGGCATTCACTGATGNGGATGCCGATTCCATCAAAATTGNTTGGGAAAAACCCACAGGG
GCAAGTTTNCANGTCNAGGNGGACCTACTCGAGCCCTGAGGATGGAATCCTTGACTNTTCCTTNNCCTGATGGG
GAAAAAAAAACCTTNAAAACTTGAAGGACCTGCCCGGGCGGCCGTNCAAAACCCAATTCCACCCCCTTGGGGGCG
TTCTATGGGNCCCACTCGGACCAAACTTGGGGTAAN

## 48 16492.edit

Fig. 15MM

# 49\_16493.edit

# 55 16496.edit

## 56 16496.edit

TCGAGCGCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCACCACG
CT

### 59 16498.edit

Fig. 15NN

# 75/101 60 16473.edit

# 60\_16498.edit

61 16499.edit

AGCGTGGTCGCGGCCGAGGTCNAGGA

62 16483.edit

TCGAGCGCCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCAACTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGTTCAAAAGACCCCTTTCGTCACCCCACCCTGGGTATG ACACTGGAAATGGTATTCAGCTTCCTGGCACTTCTGGTCAGCAACCCAGTGTTGGGCAACAAATGATCTTTGAG GAACATGGTTTTAGGCGGACCACACCGCCCACAACGGGCACCCCCCATAAGGNATAGGCCAAGACCATACCCCGC CGAATGTAGGACAAGAAGACCTTCTTCAACAACCATCTCATGGGCCCCATTCCAGGACACTTCTGAGTACATCA TTTCATGTCATCCTGGTGGGCACTTGATGAANAACCCTTACAGTTCAGGGTTCCTGGAACTTCTACCAGNGCCA CTTCTGACAGGANCTTGGGCCGNGACCACCCCT

Fig. 1500

**SUBSTITUTE SHEET (RULE 26)** 

# PCT/US01/22635

# 76/101

# 63\_16500.edit

AGCGTGGTCGCGGCCGAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCCAATCTTGTAGTTCACACCATTG
TCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTAAA
GCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGAGT
CATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCCTC
TGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTGCCCGGGCGCCCCGCT
CGA

# 64\_16493.edit

# 64\_16500.edit

Fig. 15PP

### 77/101

### 16501.edit

### 16501.2.edit

GAGGACTGGCTCAGCTCCCAGTATAGCCGCTCTCTGTCCAGTCCAGGACCAGTGGGATCAAGGCGGAGGGTGCA GATGGCGTCCACTCCAGTGGCTGCCCCATGTTTCTCAAGTCTGAGCAAAGNCAGTCTGCAGCCAGAGTACAGAG GGCCAACACTGGTGCTCTTGAACAGGGACCTGAGCAGGCCCTGAAGGACCCTCTCCGTGGTGTTGAACTTCCTG GAGCCAGGGTGCTGCATGTTCTCCTCATACCGCAGGTTGTTGATGGTGAAGTTCAGTGTGAATGGCTCCTCGCT GACCACCC

### 16502.1.edit

### 16502.2.edit

TCGAGCGCCCCCGGCCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGCCCCATGAGATGGTT GTCTGAGAGAGAGGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCCTATGCCTTATGGGGGTGGCCGTTGT GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG TGCCAGGAAGCTGAATACCATTTCCAGTGTCATACCCAGGGNGGGTGACCAAAGGGGGTCNTTTNGACCTGGNG AAAGGAACCATCCAAAANCTCTGNCCCATG

Fig. 15QQ

### 78/101

### 16503.1.edit

#### 16503.2.edit

AAGCGGCCGCCCGGGCAGGNNCAGNAGTGCCTTCGGGACTGGGNTCACCCCCAGGTCTGCGGCAGTTGTCACAG
CGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCTCC
TACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTTCC
CAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTTTA
CTTCCTCCTTCTCTACTGGAGCTTTCCGTACCTTCCACTTCTGCTGNTAGAAAAAGGGNGGAACNTCTTATCA
ATTTCATTGGACAGTANCCCNCTTTCTNCCCAAAACATNCAAGGGAAAATATTGATTNCNAGAGCGGATTAAGG
AACAACCCNAATTATGGGGGCCAGAAATAAAGGGGGCTTTTCCACAGGTNTTTTTCCT

### 16504.1.edit

TCGAGCGCCCCCGGGCAGGTCTGCAGGCTATTGTAAGTGTTCTGAGCACATATGAGATAACCTGGGCCAAGC
TATGATGTTCGATACGTTAGGTGTATTAAATGCACTTTTGACTGCCATCTCAGTGGATGACAGCCTTCTCACTG
ACAGCAGAGATCTTCCTCACTGTGCCAGTGGGCAGGAGAAAGAGCATGCTGCGACTGGACCTCGGCCGCCGACCA
CGCT

#### 16504\_2\_edit

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 15RR

**SUBSTITUTE SHEET (RULE 26)** 

### 16505.1.edit

CGAGCGGCCGCCCGGGCAGGTCCAGACTCCAATCCAGAGAACCACCAAGCCAGATGTCAGAAGCTACACCATCA CAGGTTTACAACCAGGCCACGACTACAAGATCTACCTGTACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACCCCAATTCCTTGCT GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCA GAGAAGTGCCCTCGGCCCCCGCCCTGGTGNCACAGAAGCTACTATTACTGGCCTGGAACCGGGAACCGAATAT ACAATTTATGTCATTGCCCTGAAGAAATAATCANAAGAGCGAGCCCCTGATTGGAAGG

### 16505.2.edit

### 16506.1.edit

#### 16506.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTCGGCTCAAGCTCTTGAAGGGTGGT
GTCCACCTCGAGGTCACGAAACCTGCCCGGGCGCCGCTCGA

Fig. 15SS

#### 16507.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCCGNGCCGGNCCGCTCGAAAAGCCCNAATTTCCAGNCACACTTGGCCGGCCGTT ACTACTG

### 16507.2.edit

TCGAGCGGCCGCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

## 16508.1.edit

#### 16508.2.edit

Fig. 15TT

### 16509.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCCAAGT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAAGTAACCACCACCACTCCCAAAAATGGACCAGGA
CCAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAAATGGACTATTGAAGGCTTGCAGCCCACAGTGGAA
GTATGTGGNTAGGNGTCTATGCTCAGAATCCCAAGCCGGAGAAAGTCAGCCTTCTGGTTTAGACTGCAGTAACC
AACATTGATCGCCCTAAAGGACTGGNCATTCACTTGGATGGTGGATGTCCAATTC

### 16509.2.edit

### 16510.1.edit

### 16510.2.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGACAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGTAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATGGGACCAGGA
CCAACAAAAAACTAAAACTGCANGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAG
TATGTGGGTTAGTGTCTATGCTCAGAATNCCAAGCGGAGAGAGTCAGCCTCTGGTTCAGACT

Fig. 15UU

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### 16511.1.edit

### 16511.2.edit

AGCGTGGTCGCGGCCGAGGTCTGTAGCTTCTGTGGGACTTCCACTGCTCAGGCGTCAGGCTCAGGTAGCTGCTG
GCCGCGTACTTGTTGTTGCTTTGNTTGGAGGGTGTGGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGC
CTTCCAGGCCACTGTCACGGCTCCCGGGTAGAAGTCACTTATGAGACACACCAGTGTGGCCTTGTTGGCTTGAA
GCTCCTCAGAGGAGGGTGGGAACAGAGTGACCGAGGGGGCAGCCTTGGGCTGACCTAGGACGGTCAGCTTGGTC
CCTCCGCCGAACACCCCAATTGTTGTTGCCTGCATATGAGCTGCAGTAATAATCAGCCTCATCCTCAGCCTGGAG
CCCAGAGACNGTCAAGGGAGGCCCGTGTTTGCCAAGACTTGGAAGCCAGANAAGCGATCAGGGACCCCTGAGGG
CCGCTTTACNGACCTCAAAAAATCATGAATTTGGGGGGCCCTTTTGCCTGGGNGTTGGTTAGCTAGANAACA
AAATTTCATAAAGCACCAACGTCACTGCTGGTTTCCAGTGCANGAANATGGTGAACTGAANTGTCC

### 16512.1.edit

### 16512.2.edit

TCGAGCGCCCCGGGCAGGTCCATACAGGGCTGTTGCCCAGGCCCTAGAGGNCATTCCTTGTACCCTGATCC AGAACTGTGGGACCAGCACCACCATCCGTCTACTTACCTCCCTTCGGGCCAAGCACACCCAGGAGAACTGTGAGACC TGGGGTGTAAATGGNGAGACCGGGTACTTTGGTGGACATGAGACATGAGGCATATGGGAGCCATTGGCTGNGAA GCTGCANACTTATAAGACAGCAGTGGAGACGGCAGTTCTGCTACTGCGAATTGATGACATCGTTTCAGGCCACA AAAAGAAAGGCGATGACCANAGCCGGCAAGGCGGGGCTTCCTGATGCTGACCTCGGCCGCCGACCACGCTT

Fig. 15VV

**SUBSTITUTE SHEET (RULE 26)** 

### 16514.1.edit

AGCGTGGTCGCGGCCGAGGTCCACTAGAGGTCTGTGTGCCATTGCCCAGGCAGAGTCTCTGCGTTACAAACTCC
TAGGAGGGCTTGCTGTGCGGAGGGCCTGCTATGGTGTGCTGCGGTTCATCATGAGAGTTGGGGGCCAAAGGCTGC
GAGGTTGTGGTGTCTGGGAAACTCCGAGGACAGAGGGCTAAATCCATGAAGTTTGTGGATGGCCTGATGATCCA
CAGCGGAGACCCTGTTAACTACTACGTTGACACTGCTGTGCGCCACGTGTTGCTCANACAGGGTGTGCTGGGCA
TCAAGGTGAAGATCATGCTGCCCTGGGACCCANCTGGCAAAAATGGCCCTTAAAAAACCCCTTGCCNTGACCACG
TGAACCATTTGTGNGAACCCCCAAGATGAANATACTTGCCCACCACCCCCCATTC

### 16514.2.edit

#### 16515.1.edit

#### 16515.2.edit

TCGAGCGCCCCCGGGCAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCACCAGGAAGCCCACGGGCTCC
TGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCT
TCAATCCATCCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACGA
GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT
GCCAGGAGGGCCAGACCTCGGCCGCACCACGCT

Fig. 15WW

### 16516.1.edit

ANCGTGGTCGCGGCCGAGGTCCTCACCAGAGGTGNCACCTACAACATCATAGTGGAGGCACTGAAAGACCANCAGAGGCATAAGGTTCGGGAAGAGG

### 16516.2.edit

TCGAGCGCCCCCGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGTCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCNGNCCNGAACAAC
GCTTAAGCCCGNATTCTGCAGAATAATCCCCATCACACTTGGCGGCCGCTTCGANCATGCATCNTAAAAGGGGCC
CCAATTTCCCCCTTATAAGNGAANCCGTATTTNCCAATTTCACTGGNCCCGCCGNTTTTACAAACGNCGGTGAA
CTGGGGAAAAAACCCTGGCGGTTACCCAACTTTAATCGCCNTTGGCAGCACAATCCCCCCTTTTCGNCCANCNTG
GGCGTAAATAACCGAAAA

#### 16517.1.edit

#### 

#### 16518.1.edit

### 16518.2.edit

Fig. 15XX

#### 16519.1.edit

AGCGTGGTCGCGGACGANGTCCTGTCAGAGTGGNACTGGTAGAAGTTCCANGAACCCTGAACTGTAAGGGTTCT TCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGNGNCCTGGAATGGGGCCCATGANATGGTTGC C

#### 16519.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACCGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGTTCAAAAGACCCCTTTCGGCACCCCCCTGGGTATG AACCTGGGAAAANGGNANTTAANCTTTCCTGGCA

### 16520.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCCAAGT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGGTNCCCTGGTACTGGGTTACAGANTAACCACCACCACCACAAAAATGGACCAGGA
ACCACAAAAACTTAAACTGCAGGGTCCAGATCAAAACAGAAATGACTATTGAANGCTTGCAGCCCACAGTGGGA
GTATGNGGGTAGTGNCTATGCTTCAGAATCCAAGCGGAAAAANGTCAAGCCTTNTGGGTTCAA

## 16520.2.edit

TCGAGCGGCCCCGGGCAGGTCCTTGCAGCTCTGCAGTGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT
GGATTCCATCCTCAGGGCTCGAGTAGGTCACCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT
TTGATGGAATCGACATCCACATCAGTGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGNCTGAAC
CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAANCCTT
CAATAANNCATTTCTGTTTGATCTGGACC

#### 16521.2.edit

TCGAGCGCCCCCGGCAGGTCTGGTGGGGTCCTGGCACACGCACATGGGGGNGTTGNTCTNATCCAGCTGCC CAGCCCCCATTGGCGAGTTTGAGAAGGTGTGCAGCAATGACAACAANACCTTCGACTCTTCCTGCCACTTCTTT GCCACAAAGTGCACCCTGGAGGGCACCAAAGAAGGGCCACAAGCTCCACCTGGACTACATCGGGCCTTGCAAATA CATCCCCCCTTGCCTGGACTCTGAGCTGACCGAATTCCCCCTTGCGCATGCGGGACTGGCTCAAGAACCGTCCT GGCACCCTTGTATGANAGGGATGAAGACACNACCC

# Fig. 15YY

## 16522.1.edit

### 16522.2.edit

TCGAGCGCCCCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGAAGACTGACGGTCCCCCAGGAGTTC AGGTGCTGGGCACGTTGTGAGTTTTGTCACAAGATTTTGGCCTCAACTCTCTTGTCCACCTTGGTGT TGCTGGGCCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGNGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTG CTGAGGGAGTAGAGTCCTGAGGACTGTANGACAGACCTCGGCCGNGACCACGCTAAGCCGAATTCTGCAGATAT CCATCACACTGGCGGCCGCCCGCCCAGCCATGCATTTTAGAGG

### 16523.1.edit

# AGCGTGGNCGCGGACGANGACAACACCCC

# 16523.2.edit

TCGAGCGCCCCCGGGCAGGNCCACATCGGCAGGCTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTTGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGNACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGTTCTTGACCT

### 16524.1.edit

AGCGTGGTCGCGGCCGAGGTCCAGCCTGGAGATAANGGTGAAGGTGGTGCCCCCGGACTTCCAGGTATAGCTGG ACCTCGTGGTAGCCCTGGTGAGAGAGGGGGTGAAACTGGCCCTCCAGGACCTGCTGGTTTCCCTGGTGCTCCTGGAC AGAATGGTGAACCTGGNGGTAAAGGAGAAAAGAGGGGCTCCGGNTGANAAAGGTGAAGGAGGCCCTCCTGNATTG GCAGGGGCCCCANGACTTAGAGGTGGAGCTGGCCCCCCTGGCCCCGAAGGAGGAAAGGGTGCTGCTGGTCCTCC TGGGCCACCTGG

Fig. 15ZZ

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#### 16524.2.edit

TCGAGCGCCCCCGGGCAGGTCTGGGCCAGGAGGACCAATAGGACCAGTAGGACCCCTTGGGCCATCTTTCCC
TGGGACACCATCAGCACCTGGACCGCCTGGTTCACCCTTGTCACCCTTTTGGACCAGGACTTCCAAGACCTCCTC
TTTCTCCAGGCATTCCTTGCAGACCAGGAGTACCANCAGCACCAGGTGGCCCAGGAGGACCAGCACCCTTT
CCTCCTTCGGGACCAGGGGGACCAGCTCCACCTCTAAGTCCTGGGGCCCCTGCCAATCCAGGAGGGCCTCCTTC
ACCTTTCTCACCCGGAGCCCCTCTTTCT

#### 16526.1.edit

#### 16526.2.edit

ATGCGNGGTCGCGGCCGANGACCANCTCTGGCTCATACTTGACTCTAAAGNCNTCACCAGNANTTACGGNCATT GCCAATCTGCAGAACGATGCGGGCATTGTCCGCANTATTTGCGAAGATCTGAGCCCTCAGGNCCTCGATGATCT TGAAGTAANGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCTCCAGCCTC CGGTTCTCGGTCTCCAAGNCTTCTCACTCTGTCCAGGAAAAGAGGCCAGGCGGNCGATCAGGGCTTTTGCATGG ACT

#### 16527.1.edit

#### 16527.2.edit

TCGAGCGGCCGCCCGGGCAGGTCTGCCAACACCAAGATTGGCCCCCGCCGCATCCACACAGTTNGTGTGCGGGG AGGTAACAAGAAATACCGTGCCCTGAGGNTGGACGNGGGGGAATTTCTCCCTGGGGCTCAGAGTGTTGTACTCGTA AAACAAGGATCATCGATGTTGTCTACAATGCATCTAATAACGAGCTGGTTCGTACCAAGACCCTGGTGAAGAAT TGCATCGTGCTCATNGACAGCACACCGTACCGACAGTGGGTACCGAAGTCCCACTATGCNCCT

## Fig. 15AAA

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#### 16528.1.edit

TCGAGCGGCCGCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCCTGAAG

#### 16528.2.edit

AGCGTGNTCNCGGCCGAGGATGGGGAAGCTCGNCTGTCTTTTTCCTTCCAATCAGGGGCTNNNTCTTCTGATTA
TTCTTCAGGGCAANGACATAAATTGTATATTCGGNTCCCGGTTCCAGNCCAGTAATAGTAGCCTCTGTGACACC
AGGGCGGGCCCGAGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGAAGCCGGTAATCC
TGGCACGTGGGCGGCCGCTGCCATGATACCACCAANGAATTGGGTGTGGACCTGCCCGGGCGGCCGCTCGAAA
ANCCGAATTCNTGCAAGAATATCCATCACACTTGGGCGGCCGGTCGAACCCATGCATCNTAAAAGGGCCCCCAAT
TTCCCCCCTATTAGGNGAAGCCNCATTTAACAAATTCCACTTGG

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#### 16529.2.edit

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Fig. 15BBB

WO 02/06317 PCT/US01/22635

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#### 16530.1.edit

#### 16530.2.edit

#### 16531.1.edit

#### 16531.2.edit

#### 16532.1.edit

Fig. 15CCC

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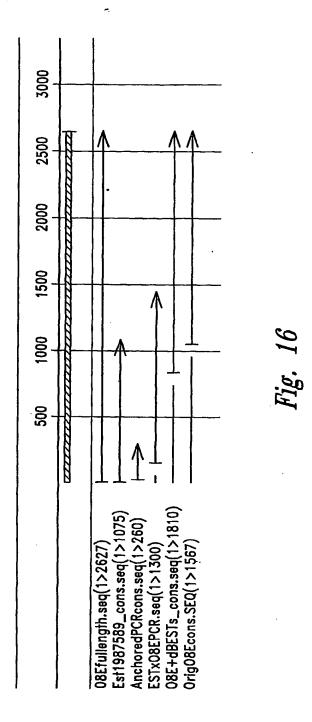
Fig. 15DDD

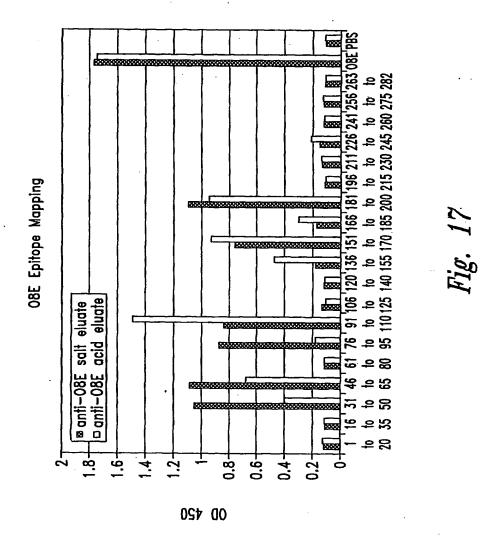
**SUBSTITUTE SHEET (RULE 26)** 

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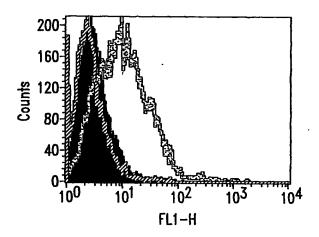
Fig. 15EEE





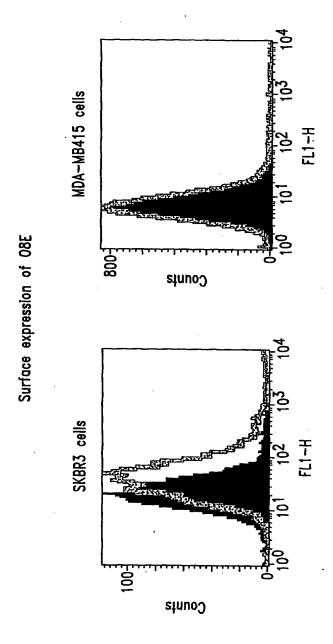
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**OBE Surface Expression** 



- B305D/HEK stained with anti-08E antibody
- --- 08E/HEK stained with anti-08E antibody
- OBE/HEK stained with an irrelevant antibody

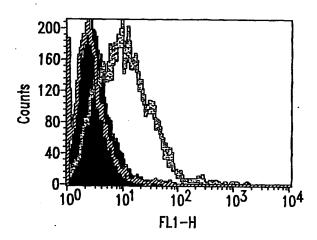
Fig. 18



Black; irrelevant antibody Light gray; anti-08E antibody

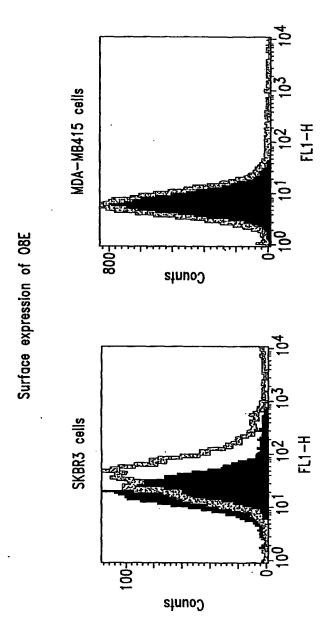
Fig. 19

**O8E Surface Expression** 



- B305D/HEK stained with anti-08E antibody
- --- O8E/HEK stained with anti-08E antibody
- 08E/HEK stained with an irrelevant antibody

Fig. 20



Black; Irrelevant antibody Light Grey; Anti-08E antibody

Fig. 21

O8E expression in HEK293 Cells (probed with anti-08E rabbit polyclonal sera #2333L)

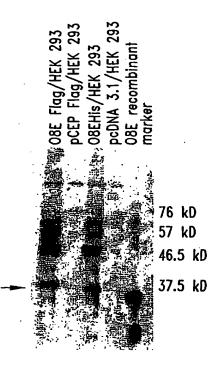


Fig. 22

99/101

Fig. 23

	99/101												
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)  urlion	1:128000	999	90.0	9.9	<u>=</u>	8	 6.	6.0	0.07	0.07	0.92	9.88	0.90
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Antigen	on Plate	380	#632-24)										

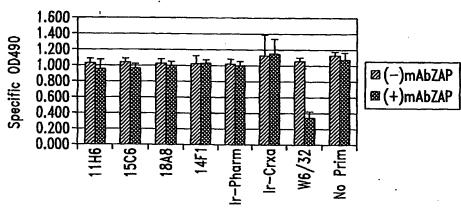
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affi-pure 08E #2576L 739.87A&B

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Date: 5/2/2000		<del></del>		ı	739.87A ncentration 1.4mg/ml	18mg	Sera Sample		preimmune sera (2576L)		Average	-08E (2576K):2/8/2000		Average	affinity pure a-08E poly	salt peak 739-87A	Average	affinity pure a-08E poly	acid peak 739-67B	
	08E polyclonal 2576L, 1/11/2000	affinity	PBS	#705, p150				1:1000	0.15	0.14	0.14	2.74	2.72	2.73	. 69.7	2.59	2.64	2.46	2.65	
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					7	3		4900	0.09	0.09	0.09	2.63	2.64	2.63	2.50	2.38	244	2.40	7.61	
					739.87B 1.7mg/ml	3mg		1	9.08	90:0	90.0	2.49	2.47	2.48	2.21	2.21	2.21	2.34	2.45	
			•		m.Ē			1:16000	0.08	0.07	0.07	2.29	2.26	777	1.83	1.82	1.83	208	2.14	
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Primary Ab (50ng/well)

## Hek/O8E Internalization of O8E mAbs

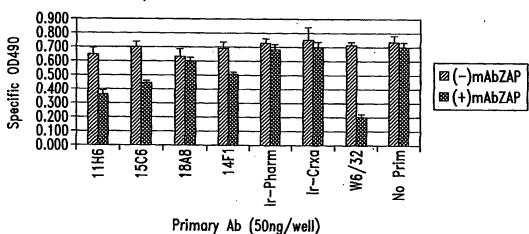


Fig. 25

1

#### SEQUENCE LISTING

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 Algate, Paul A.
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<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

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<213> Homo sapiens
<400> 15
atctcttgta tgccaaatat ttaatataaa tctttgaaac aagttcagat gaaataaaaa 60
tcaaagtttg caaaaacgtg aagattaact taattgtcaa atattcctca ttgccccaaa 120
tcagtatttt ttttatttct atgcaaaagt atgccttcaa actgcttaaa tgatatatga 180
tatgatacac aaaccagttt tcaaatagta aagccagtca tcttgcaatt gtaagaaata 240
ggtaaaagat tataagacac cttacacaca cacacacaca cacacacgtg tgcacgccaa 300
tgacaaaaaa caatttggcc tctcctaaaa taagaacatg aagaccctta attgctgcca 360
```

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ggagggaaca ctgtgtcacc cctccctaca atccaggtag tttcctttaa tccaatagca 420
aatetgggea tatttgagag gagtgattet gacagecaeg ttgaaateet gtggggaaee 480
atteatgtcc acceactggt gccctgaaaa aatgccaata atttttcgct cccacttctg 540
etgetgtete ttecacatee teacatagae eccagaceeg etggeecetg getgggeate 600
gcattgctgg tagagcaagt cataggtctc gtctttgacg tcacagaagc gatacaccaa 660
attgcctggt cggtcattgt cataaccaga ga
<210> 16
<211> 728
<212> DNA
<213> Homo sapiens
<400> 16
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cctgccttgg cctcccaaag tgctgggatt acaggcataa gccactgcgc ccggctgatc 120
tgatggtttc ataaggcttt tccccctttt gctcagcact tctccttcct gccgccatgt 180
gaagaaggac atgtttgctt ccccttccac cacgattgta agttgtttcc tgaggcctcc 240
ccggccatgc tgaactgtga gtcaattaaa cctctttcct ttataaatta tccagttttg 300
ggtatgtctt tattagtaga atgagaacag actaatacaa cccttaaagg agactgacgg 360
agaggattet teetggatee cageacttee tetgaatget aetgacatte ttettgagga 420
ctttaaactg ggagatagaa aacagattcc atggctcagc agcctgagag cagggaggga 480
gccaagctat agatgacatg ggcagcctcc cctgaggcca ggtgtggccg aacctgggca 540
gtgctgccac ccaccccacc agggccaagt cctgtccttg qaqaqccaag cctcaatcac 600
tgctagcctc aagtgtcccc aagccacagt ggctaggggg actcagggga cagttcccag 660
tetgecetae ttetettaee tttacecete atacetecaa agtagaceat gttcatgagg 720
tccaaagg
                                                                   728
<210> 17
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 518, 528
<223> n = A, T, C or G
<400> 17
aagcgaggaa gccactgcgg ctcctggctg aaaagcggcg ccaggctcgg gaacagaggg 60
aacgcgaaga acaggagcgg aagctgcagg ctgaaaggga caagcgaatg cgagaggagc 120
agetggeeeg ggaggetgaa geeegggetg aacgtgagge egaggegegg agaegggagg 180
agcaggagge tegagagaag gegeaggetg agcaggagga geaggagega etgeagaage 240
agaaagagga agccgaagcc cggtcccggg aagaagctga gcgccagcgc caggagcggg 300
aaaagcactt tcagaaggag gaacaggaga gacaagagcg aagaaagcgg ctggaggaga 360
taatgaagag gactcggaaa tcagaagccg ccgaaaccaa gaagcaggat gcaaaggaga 420
ccgcagctaa caattccggc ccagaccett gtgaaagctg tagagactcg gccctctggg 480
cttccagaaa ggattctatt gcagaaagga aggagctngg ccccccanqq a
                                                                   531
<210> 18
<211> 1041
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 544
<223> n = A, T, C or G
```

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<400> 18
ctctgtggaa aactgatgag gaatgaattt accattaccc atgttctcat ccccaaqcaa 60
agtgctgggt ctgattactg caacacagag aacgaagaag aacttttcct catacaggat 120
cagcagggcc tcatcacact gggctggatt catactcacc ccacacagac cgcgtttctc 180
tecagtgteg acetacaeac teactgetet taccagatga tgttgccaga gtcagtagec 240
attgtttgct cccccaagtt ccaggaaact ggattcttta aactaactga ccatggacta 300
gaggagattt cttcctgtcg ccagaaagga tttcatccac acagcaagga tccacctctg 360
ttctgtagct gcagccacgt gactgttgtg gacagagcag tgaccatcac agaccttcga 420
tgagcgtttg agtccaacac cttccaagaa caacaaaacc atatcagtgt actgtagccc 480
cttaatttaa gctttctaga aagctttgga agtttttgta gatagtagaa aggggggcat 540
cacntgagaa agagctgatt ttgtatttca ggtttgaaaa gaaataactg aacatatttt 600
ttaggcaagt cagaaagaga acatggtcac ccaaaagcaa ctgtaactca gaaattaagt 660
tactcagaaa ttaagtagct cagaaattaa gaaagaatgg tataatgaac ccccatatac 720
cetteettet ggatteacea attgttaaca tttttteet eteagetate ettetaattt 780
ctctctaatt tcaatttgtt tatatttacc tctgggctca ataagggcat ctgtgcagaa 840
atttggaagc catttagaaa atcttttgga ttttcctgtg gtttatggca atatgaatgg 900
agettattae tggggtgagg gacagettae tecatttgae cagattgttt ggctaacaca 960
tcccgaagaa tgattttgtc aggaattatt gttatttaat aaatatttca ggatattttt 1020
cctctacaat aaagtaacaa t
<210> 19
<211> 1043
<212> DNA
<213> Homo sapiens
<400> 19
ctctgtggaa aactgatgag gaatgaattt accattaccc atgttctcat ccccaagcaa 60
agtgctgggt ctgattactg caacacagag aacgaagaag aacttttcct catacaggat 120
cagcagggcc tcatcacact gggctggatt catactcacc ccacacagac cgcgtttctc 180
tecagtgteg acctacacac teactgetet taccagatga tgttgccaga gtcagtagec 240
attgtttgct cccccaagtt ccaggaaact ggattcttta aactaactga ccatggacta 300
gaggagattt cttcctgtcg ccagaaagga tttcatccac acagcaagga tccacctctg 360
ttetgtaget geageeacgt gactgttgtg gacagageag tgaccateac agacettega 420
tgagcgtttg agtccaacac cttccaagaa caacaaaacc atatcagtgt actgtagccc 480
cttaatttaa gctttctaga aagctttgga agtttttgta gatagtagaa aggggggcat 540
cacctgagaa agagctgatt ttgtatttca ggtttgaaaa gaaataactg aacatatttt 600
ttaggcaagt cagaaagaga acatggtcac ccaaaagcaa ctgtaactca gaaattaagt 660
tactcagaaa ttaagtagct cagaaattaa gaaagaatgg tataatgaac ccccatatac 720
ccttccttct ggattcacca attgttaaca tttttttcct ctcagctatc cttctaattt 780
ctctctaatt tcaatttgtt tatatttacc tctgggctca ataagggcat ctgtgcagaa 840
atttggaagc catttagaaa atcttttgga ttttcctgtg gtttatggca atatgaatgg 900
agcttattac tggggtgagg gacagcttac tccatttgac cagattgttt ggctaacaca 960
tcccgaagaa tgattttgtc aggaattatt gttatttaat aaatatttca ggatattttt 1020
cctctacaat aaagtaacaa tta
<210> 20
<211> 448
<212> DNA
<213> Homo sapiens
<400> 20
ggacgacaag gccatggcga tatcggatcc gaattcaagc ctttggaatt aaataaacct 60
ggaacaggga aggtgaaagt tggagtgaga tgtcttccat atctatacct ttgtgcacag 120
ttgaatggga actgtttggg tttagggcat cttagagttg attgatggaa aaagcagaca 180
ggaactggtg ggaggtcaag tggggaagtt ggtgaatgtg gaataactta cctitgtgct 240
ecaettaaac cagatgtgtt geagetttee tgacatgeaa ggatetaett taatteeaca 300
ctctcattaa taaattgaat aaaagggaat gttttggcac ctgatataat ctgccaggct 360
atgtgacagt aggaaggaat ggtttcccct aacaagccca atgcactggt ctgactttat 420
```

```
aaattattta ataaaatgaa ctattatc
                                                                   448
<210> 21
<211> 411
<212> DNA
<213> Homo sapiens
<400> 21
ggcagtgaca ttcaccatca tgggaaccac cttccctttt cttcaggatt ctctgtagtg 60
gaagagagca cccagtgttg ggctgaaaac atctgaaagt agggagaaga acctaaaata 120
atcagtatct cagagggctc taaggtgcca agaagtctca ctggacattt aagtgccaac 180
aaaggcatac tttcggaatc gccaagtcaa aactttctaa cttctgtctc tctcagagac 240
aagtgagact caagagtcta ctgctttagt ggcaactaca gaaaactggt gttacccaga 300
aaaacaggag caattagaaa tggttccaat atttcaaagc tccgcaaaca ggatgtgctt 360
tcctttgccc atttagggtt tcttctcttt cctttctctt tattaaccac t
<210> 22
<211> 896
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 230, 320
<223> n = A, T, C or G
<400> 22
tgcgctgaaa acaacggcct cctttactgt taaaatgcag ccacaggtgc ttagccgtgg 60
gcatetcaac caccagecte tgtggggggc aggtgggcgt eeetgtgggc etetgggece 120
acgtecagee tetgteetet geetteegtt ettegacagt gtteceggea teeetggtea 180
cttggtactt ggcgtgggcc tcctgtgctg ctccagcagc tcctccaggn ggtcggcccg 240
cttcaccgca gcctcatgtt gtgtccggag gctgctcacg gcctcctcct tcctcgcgag 300
ggctgtcttc accetceggn gcacctcetc cagetceage tgctggcggg cctgcagegt 360
ggccagetcg gccttggcct gccgcgtctc ctcctcarag gctgccagec ggtcctcgaa 420
ctcctggcgg atcacctggg ccaggttgct gcgctcgcta gaaagctgct cgttcaccgc 480
etgegeatee tecagegeee geteettetg eegeacaagg ecetgeagae geagattete 540
geceteggee tececaaget ggeeetteag eteegageae egeteetgaa getteegete 600
egactgetee ageteggaga geteggeete gtaettgtee egtaageget tgatgegget 660
ctcggcagcc ttctcactct cctccttggc cagcgccatg tcggcctcca gccggtgaat 720
gaccagetea ateteettgt eceggeettt eeggatttet teeeteaget eetgtteeeg 780
gttcagcage cacgcctcct ccttcctggt gcggccggcc tcccacgcct gcctctccag 840
ctccagctgc tgcttcaggg tattcagctc catctggcgg gcctgcagcg tggcca
<210> 23
<211> 111
<212> DNA
<213> Homo sapiens
<400> 23
caacttatta cttgaaatta taatatagcc tgtccgtttg ctgtttccag gctgtgatat 60
attttcctag tggtttgact ttaaaaataa ataaggttta attttctccc c
<210> 24
<211> 531
<212> DNA
<213> Homo sapiens
<220>
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```
<221> misc feature
<222> 472, 494
<223> n = A, T, C \text{ or } G
<400> 24
tgcaagtcac gggagtttat ttatttaatt tttttcccca gatggagact ctgtcgccca 60
ggctggagtg caatggtgtg atcttggctc actgcaacct ccacctcctg ggttcaagcq 120
attetectge cacageetee egagtagetg ggattacagg tgeeegeeae cacacecage 180
taatttttat atttttagta aagacagggt ttccccatgt tggccaggct ggtcttgaac 240
ttctgacctc aggtgatcca cctgcctcgg cctcccaaag tgttgggatt acaggcgtga 300
getaccegtg cetggecage caetggagtt taaaggacag teatgttgge tecageetaa 360
ggcggcattt tcccccatca gaaagcccgc ggctcctqta cctcaaaata gggcacctgt 420
aaagteagte agtgaagtet etgetetaae tggceaeceg gggeeattgg entetgaeae 480
agccttgcca ggangcctgc atctgcaaaa gaaaagttca cttcctttcc g
<210> 25
<211> 471
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 377
<223> n = A, T, C \text{ or } G
<400> 25
cagagaatct kagaaagatg tcgcgttttc ttttaatgaa tgagagaagc ccatttgtat 60
ccctgaatca ttgagaaaag gcggcggtgg cgacagcggc gacctaggga tcgatctgga 120
gggacttggg gagcgtgcag agacctctag ctcgagcgcg agggacctcc cgccgggatg 180
cctggggagc agatggaccc tactggaagt cagttggatt cagatttctc tcagcaagat 240
actecttgee tgataattga agatteteag cetgaaagee aggttetaga ggatgattet 300
ggttctcact tcagtatgct atctcgacac cttcctaatc tccagacgca caaaqaaaat 360
cctgtgttgg atgttgngtc caatccttga acaaacagct ggagaagaac gaggagaccg 420
gtaatagtgg gttcaatgaa catttgaaag aaaaccaggt tgcagaccct g
<210> 26
<211> 541
<212> DNA
<213> Homo sapiens
<400> 26
gactgtcctg aacaagggac ctctgaccag agagctgcag gagatgcaga gtggtggcag 60
gagtggaagc caaagaacac ccaccttcct cccttgaagg agtagagcaa ccatcagaag 120
atactgtttt attgctctgg tcaaacaagt cttcctgagt tgacaaaacc tcaggctctg 180
gtgacttctg aatctgcagt ccactttcca taagttcttg tgcagacaac tgttcttttg 240
cttccatagc agcaacagat gctttggggc taaaaggcat gtcctctgac cttgcaggtg 300
gtggattttg ctcttttaca acatgtacat ccttactggg ctgtgctgtc acagggatgt 360
cettgetgga etgttetget atggggatat ettegttgga etgttettea tgettaattg 420
cagtattagc atccacatca gacagcctgg tataaccaga gttggtggtt actgattgta 480
gctgctcttt gtccacttca tatggcacaa gtattttcct caacatcctg gctctgggaa 540
<210> 27
<211> 461
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc_feature
<222> 367
<223> n = A, T, C or G
<400> 27
gaaatgtata tttaatcatt ctcttgaacg atcagaactc traaatcagt tttctataac 60
arcatgtaat acagtcaccg tggctccaag gtccaggaag gcagtggtta acacatgaag 120
agtgtgggaa gggggctgga aacaaagtat tcttttcctt caaagcttca ttcctcaagg 180
cctcaattca agcagtcatt gtccttgctt tcaaaagtct gtgtgtgctt catggaaggt 240
atatgtttgt tgccttaatt tgaattgtgg ccaggaaggg tctggagatc taaattcaga 300
gtaagaaaac ctgagctaga actcaggcat ttctcttaca gaacttggct tgcagggtag 360
aatgaangga aagaaactta gaagctcaac aagctgaaga taatcccatc aggcatttcc 420
cataggcctt gcaactctgt tcactgagag atgttatcct g
<210> 28
<211> 541
<212> DNA
<213> Homo sapiens
<400> 28
agtetggagt gagcaaacaa gagcaagaaa caarragaag ccaaaagcag aaggetecaa 60
tatgaacaag ataaatctat cttcaaagac atattagaag ttgggaaaat aattcatgtg 120
aactagacaa gtgtgttaag agtgataagt aaaatgcacg tggagacaag tgcatcccca 180
gateteaggg aceteceet geetgteace tggggagtga gaggacagga tagtgeatgt 240
tetttgtete tgaattttta gttatatgtg etgtaatgtt getetgagga ageceetgga 300
aagtotatoo caacatatoo acatottata ttocacaaat taagotgtag tatgtaccot 360
aagacgctgc taattgactg ccacttcgca actcaggggc ggctgcattt tagtaatggg 420
tcaaatgatt cactttttat gatgcttccc aaggtgcctt ggcttctctt cccaactgac 480
aaatgcccaa gttgagaaaa atgatcataa ttttagcata aaccgagcaa tcggcgaccc 540
<210> 29
<211> 411
<212> DNA
<213> Homo sapiens
<400> 29
tagctgtctt cctcactctt atggcaatga ccccatatct taatggatta agataatgaa 60
agtgtatttc ttacactctg tatctatcac cagaagctga ggtgatagcc cgcttgtcat 120
tgtcatccat attctgggac tcaggcggga actttctgga atattgccag ggagcatggc 180
agaggggcac agtgcattct ggggggaatgc acattggctc agcctgggta atgagtgata 240
tacattacct ctgttcacaa ctcattgccc agcaccagtc acaaggcccc accaaatacc 300
agagcccaag aaatgtagtc ctgttgatat ggttttgctg tgtcccaacc caaatctcat 360
cttgaattgt aagctcccat aattcccatg tgttgtggga gggacctggt g
<210> 30
<211> 511
<212> DNA
<213> Homo sapiens
<400> 30
atcatgagga tgttaccaaa gggatggtac taaaccattt gtattcgtct gttttcacac 60
tgctttgaag atactacctg agactgggta atttataaac aaaagagatt taattgactc 120
acagttctgc atggctgaag aggcctcagg aaacttacag tcatggtgga aggcaaagga 180
ggagcaaggc atgtcttaca tgtcagtagg agagagagcg agagcaggag aacctgccac 240
ttataaacca ttcagatctc ataactccct atcatgagaa aaacatggag gaaaccaccc 300
tcatgatcca atcacctccc gccaggtccc tccctcgaca cgtggggatt ataattcagg 360
attagaggga cacagagaca aaccatatca tcattcatga gaaatccacc ctcatagtcc 420
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```
aatcagctcc taccaggccc cacctccaac actggggatt gcaattcaac atgagatttg 480
 gatggggaca cagattcaaa ccatatcata c
 <210> 31
 <211> 827
 <212> DNA
 <213> Homo sapiens
<400> 31
 catggccttt ctccttagag gccagaggtg ctgccctggc tgggagtgaa gctccaggca 60
 ctaccagett teetgatttt ecegtttggt ecatgtgaag agetaccaeg agecceagee 120
 tcacagtgtc cactcaaggg cagcttggtc ctcttgtcct gcagaggcag gctggtgtga 180
 ccctgggaac ttgacccggg aacaacaggt ggcccagagt gagtgtggcc tggccctca 240
 acctagtgtc cgtcctcctc tctcctggag ccagtcttga gtttaaaggc attaagtgtt 300
 agatacaagc teettgtgge tggaaaaaca eeeetetget gataaagete agggggeact 360
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 tecetetygt geteceacgt etgtteetea ecetecatet etgggageag etgeacetga 480
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 tggcttacaa agtagagttg gcccagtttc cttccacctg aggggagcac tctgactcct 600
 aacagtette ettgeeetge cateatetgg ggtggetgge tgteaagaaa ggeegggeat 660
 getttetaaa cacagecaca ggaggettgt agggeatett ceaggtgggg aaacagtett 720
 agataagtaa ggtgacttgc ctaaggcctc ccagcaccct tgatcttgga gtctcacaqc 780
 agactgcatg tsaacaactg gaaccgaaaa catgcctcag tataaaa
 <210> 32
 <211> 291
 <212> DNA
 <213> Homo sapiens
 <400> 32
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 ttggatgacc tctagagaaa ttgcccaaga agcccacctt ctggtcccaa cctgcagacc 120
 ccacagcagt cagttggtca ggccctgctg tagaaggtca cttggctcca ttgcctgctt 180
 ccaaccaatg ggcaggagag aaggeettta tttctcgccc acccattctc ctgtaccagc 240
 acctccgttt tcagtcagyg ttgtccagca acggtaccgt ttacacagtc a
 <210> 33
 <211> 491
 <212> DNA
 <213> Homo sapiens
 <400> 33
 tgcatgtagt tttatttatg tgttttsgtc tggaaaacca agtgtcccag cagcatgact 60
 gaacatcact cacttcccct acttgatcta caaggccaac gccgagagcc cagaccagga 120
 ttecaaacac actgcacgag aatattgtgg atccgctgtc aggtaagtgt ccgtcactga 180
 cccaracgct gttacgtggc acatgactgt acagtgccac gtaacagcac tgtacttttc 240
 tcccatgaac agttacctgc catgtatcta catgattcag aacattttga acagttaatt 300
 ctgacacttg aataatccca tcaaaaaccg taaaatcact ttgatgtttg taacgacaac 360
 atagcatcac tttacgacag aatcatctgg aaaaacagaa caacgaatac atacatctta 420
 aaaaatgctg gggtgggcca ggcacagctt cacgcctgta atcccagcac tttgggaggc 480
 ttaagcgggt g
                                                                    491
 <210> 34
 <211> 521
 <212> DNA
 <213> Homo sapiens
 <220>
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```
<221> misc_feature
<222> 453, 476, 487
<223> n = A,T,C or G
<400> 34
tggggcggaa agaagccaag gccaaggagc tggtgcggca gctgcagctg gaggccgagg 60
agcagaggaa gcagaagaag cggcagagtg tgtcgggcct gcacagatac cttcacttgc 120
tggatggaaa tgaaaattac ccgtgtcttg tggatgcaga cggtgatgtg atttccttcc 180
caccaataac caacagtgag aagacaaagg ttaagaaaac gacttctgat ttgtttttgg 240
aagtaacaag tgccaccagt ctgcagattt gcaaggatgt catggatgcc ctcattctga 300
aaatqqcaag aaatgaaaaa gtacacttta gaaaataaag aggaaggatc actctcagat 360
actgaagccg atgcagtete tggacaactt ccagatecca caacgaatee cagtgetgga 420
aaggacgggc ccttccttct ggtggtggaa cangtcccgg tggtggatct tggaanggaa 480
cctgaangtg gtgtaccccg tccaaggccg accttggcca c
<210> 35
<211> 161
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 18
<223> n = A, T, C or G
<400> 35
teccgegete geagggeneg tgccacetge cygtecqcce geteqeteqe teqeceqeeq 60
egeegegetg cegacegyea geatgetgee gagagtggge tgeecegege tgeegetgee 120
geogeogeog etgetgeege tgetgeeget getgetgetg e
<210> 36
<211> 341
<212> DNA
<213> Homo sapiens
<400> 36
ggcgggtagg catggaactg agaagaacga agaagctttc agactacgtg gggaagaatg 60
aaaaaaccaa aattatcgcc aagattcagc aaaggggaca gggagctcca gcccgagagc 120
ctattattag cagtgaggag cagaagcagc tgatgctgta ctatcacaga agacaagagg 180
ageteaagag attggaagaa aatgatgatg atgeetattt aaacteacca tgggeggata 240
acactgcttt gaaaagacat tttcatggag tgaaagacat aaagtggaga ccaagatgaa 300
gttcaccagc tgatgacact tccaaagaga ttagctcacc t
                                                                   341
<210> 37
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 516
<223> n = A, T, C or G
<400> 37
tctgaaggtt aaatgtttca tctaaatagg gataatgrta aacacctata gcatagagtt 60
gtttgagatt aaatgagata atacatgtaa aattatgtgc ctggcataca gcaagattgt 120
tgttgttgtt gatgatgatg atgatgatga taatatttt ctatccccag tgcacaactg 180
cttgaaccta ttagataatc aatacatgtt tcttgaactg agatcaattt ccccatgttg 240
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ctccattagc tctcatctca ccagcccatc attattgtat gtgctgcctt ctgaagcttg 420
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<211> 461
<212> DNA
<213> Homo sapiens
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gattteetta gtggtgtate taateaeagg aaacatetgt ggtteeetee agtetettte 180
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<212> DNA
<213> Homo sapiens
<400> 40
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cctttacgca ggaaacaggg cttggaactt ctaagggaaa ttaacatgca ccaccacat 240
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<210> 41
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<212> DNA
<213> Homo sapiens
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<211> 381
<212> DNA
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<400> 42
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<212> DNA
<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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<210> 45
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<212> DNA
<213> Homo sapiens
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<210> 46
<211> 481
<212> DNA
<213> Homo sapiens
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cttectgeaa ateacacaca catgegggee acacatacet getgeeetgg agatggggaa 180
gtaggagaga tgaatagagg cccatacatt gtacagaagg aggggcaggt gcagataaaa 240
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<210> 47
<211> 461
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 128
<223> n = A, T, C or G
<400> 47
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<210> 48
<211> 571
<212> DNA
<213> Homo sapiens
<400> 48
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cccgtgccag gtacttcacg caccaagctc a
<210> 49
<211> 511
<212> DNA
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<210> 50
<211> 561
<212> DNA
<213> Homo sapiens
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gaattttggc caggcatggt g
<210> 51
<211> 451
<212> DNA
<213> Homo sapiens
<400> 51
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cttaggtctg tattcagtca ttcagcatgt agatactaaa aatatactgt agtgttcctt 180
taaggaagac tgtacagggt gtgttgcaag atgacattca ccaatttgtg aattatttca 240
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gagagatgca cacaaaaatg ttacataaaa gttcagacat tctaatgata agtgaactga 360
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<210> 52
<211> 682
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<212> DNA
<213> Homo sapiens
<400> 52
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<210> 53
<211> 311
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 208
<223> n = A, T, C or G
<400> 53
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tetgeattwa teacattaaa aatggettte ttggaaaate ttettgatat gaataaagga 180
tettttavag ccatcattta aagcmggntt etetecaaca egagtetget sasggggggk 240
gagctgtgaa ctctggctga aggctttccc atacacactg caatgacmtg gtttctgacc 300
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<210> 54
<211> 561
<212> DNA
<213> Homo sapiens
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gagagactcg taagtgcaga aaacatggtc cagcctttgt tcatggctcc agcctcacag 480
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<210> 55
<211> 811
<212> DNA
<213> Homo sapiens
<400> 55
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cctgttgcct gacaaatgga attgacagcg tatgccatga ctattccatt tgtcaggcat 660
acgctgtcaa tttttccacc aatcccttgt ctctctttgg agagatcttc ttatcagcta 720
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gaacccctgg gaccaggact aaaacctcca g
<210> 56
<211> 591
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 45, 477, 490, 561
<223> n = A, T, C or G
<400> 56
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<211> 481
<212> DNA
<213> Homo sapiens
<400> 57
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<212> DNA
<213> Homo sapiens
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<211> 191
<212> DNA
<213> Homo sapiens
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ccttacaagt gtaatgagtg tggcaaagcc tttggcaagc agtcaacact tattcaccat 180
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<212> DNA
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<210> 61
<211> 381
<212> DNA
<213> Homo sapiens
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<210> 62
<211> 906
<212> DNA
<213> Homo sapiens
<400> 62
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taggggaagg geoegegtag teetegeagg geoecagage tggagtegge teeacagece 180
egggeegteg getteteact teetggaeet eeeggegee egggeetgag gaetggeteg 240
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agegteegga gggaagaaga acetgggeta eegteetgge etteecmeee eetteeeggg 420
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<211> 356
<212> DNA
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<213> Homo sapiens
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 <222> 7, 346, 350, 353
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 <211> 226
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 <213> Homo sapiens
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<213> Homo sapiens
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<210> 85

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<211> 561
<212> DNA
<213> Homo sapiens
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<210> 86
<211> 795
<212> DNA
<213> Homo sapiens
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<211> 594
<212> DNA
<213> Homo sapiens
<400> 87
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<212> DNA
<213> Homo sapiens
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<210> 89
<211> 561
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> 544, 551
<223> n = A, T, C or G
<400> 89
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<213> Homo sapiens
<400> 90
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<211> 541
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 480, 491
<223> n = A, T, C or G
<400> 91
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<211> 551
<212> DNA
<213> Homo sapiens
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<212> DNA
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<223> n = A, T, C or G
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gagattgtcc ctaagtaact gcatgatcag agtgctgkct ttataagact cttcattcag 180
cgtatccaat tcagcaattg cttcatcaaa tgccgttttt gccaggctac aggccttttc 240
aggagagttt agaatctcat agtaaaagac tgagaaattt agtgccagac caagacgaat 300
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tgggtgtgta ggctgcattn ctttcttact aatttcaaat gcttcctggt aagcctqctq 360
ggagttcgac acaagtggtt tgtttgttgc tccagatgcc acttcagaaa qatacctaaa 420
ataatctcct ttcattttca aagtagaaca c
<210> 118
<211> 501
<212> DNA
<213> Homo sapiens
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gggtctttgt tccctgcagc cctcccacgg gaatgacaat ggataaaagt gagctggtac 180
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gaaaacagag aggaatgaga agaaqcaqca qatqqqcaaa qaqtaccqtq aqaaqataqa 420
ggcagaactg caggacatct gcaatgatgt tctggagctt gttggacaaa tatcttattc 480
caatgctaca caacccagaa a
<210> 119
<211> 391
<212> DNA
<213> Homo sapiens
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agggttcccc tetectetgg ggactgacte aaacactgat gtggcagtat acaccattce 180
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tototgatca ggggaaagga gotogaatga gggaggtaga gttggaaagg gaaaggatto 360
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<211> 421
<212> DNA
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<220>
<221> misc feature
<222> 409
<223> n = A, T, C or G
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caccgagget gagageaeca tgaacgacet cgtetetgag tateaageag taccaggatg 180
ccaccgcaga agaggaggag gatttcgqtg aggaggccga agaggaggcc taaggcagag 240
cccccatcac ctcaggette teagtteect tageegtett acteaactge ccettteete 300
teeeteagaa titgtgttig eigeetetat eitgtittit gittitett eigggggggt 360
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<210> 121
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<212> DNA
<213> Homo sapiens
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<400> 121
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agccacaaaa ctgtaacctc aaggaaacca taaagcttgg agtgccttaa tttttaacca 180
gtttccaata aaacggttta ctacct
<210> 122
<211> 131
<212> DNA
<213> Homo sapiens
<400> 122
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gatgacgatg tcgataccaa gaagcagaag accgacgagg atgactagac agcaaaaaag 120
gaaaagttaa a
<210> 123
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 166, 202, 222, 225
<223> n = A, T, C or G
<400> 123
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cctcagtggc agtakgctaa kgaagatcaa gctacagsac atyatctaat atgaatgtta 120
gcaattacat akcargaage atgtttgett tecagaagae tatggnacaa tggteattwg 180
ggcccaagag gatatttggc cnggaaagga tcaagataga tnaangtaaa g
<210> 124
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 284, 412, 513
<223> n = A, T, C or G
<400> 124
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atetteagea ggeageteee accaggaett ateteasaaa attgetgaee geetgggeet 180
ggagctaggc aaggtggtga ctaagaaatt cagcaaccag gagacctgtg tggaaattgg 240
tgaaagtgta ccgtggagag gatgtctaca ttgttcagag tggntgtggc gaaatcaatg 300
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ttactgcagt catcccatgc ttcccttatg ccccggcagg ataagaaaga tnagagccgg 420
gccgccaatc tcagccaagc ttggtgcaaa tatgctatct gtagcagtgc agatcatatt 480
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                                                                   521
<210> 125
<211> 341
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> 277
<223> n = A, T, C or G
<400> 125
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tgtggcatct gcagctggga agagagaggc cggggaggtg ccgagctcgg tgctggtctc 180
tttccaaata taaatacgtg tgtcagaact ggaaaatcct ccagcaccca ccacccaagc 240
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<210> 126
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 353, 399, 455
<223> n = A, T, C or G
<400> 126
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caggcccaga gtggcactgg acagaccatg caggtgatgc agcagatcat cactaacaca 120
ggagagatcc agcagatccc ggtgcagctg aatgccggcc agctgcagta tatccgctta 180
gcccagcctg tatcaggcac tcaagttgtg cagggacaga tccagacact tgccaccaat 240
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aagatggaca gcagctctac cagatccagc aagtcaccat gcctgcgggc cangacctcg 360
ccageccatg ttcatccagt caagecaace agecettena egggeaggee ecceaggtga 420
ccggcgactg aagggcctga gctggcaagg ccaangacac ccaacacaat ttttgccata 480
cagececcag geaatgggea cageetttet teccagagga e
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<210> 127
<211> 351
<212> DNA
<213> Homo sapiens
<400> 127
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gtccctggga gaaaagagtg tggcaatgaa tccacccact ctccacaggg aataaatctg 180
tctcttaaat gcaaagaatg tttccatggc ctctggatgc aaatacacag agctctgggg 240
tcagagcaag ggatggggag aggaccacga gtgaaaaagc agctacacac attcacctaa 300
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<211> 521
<212> DNA
<213> Homo sapiens
<400> 128
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agagttaagg gaaggtttcc tttcattcct gttccttctc ttttgctttt gaacagtttt 120
taaatatact aatagctaag tcatttgcca gccaggtccc ggtgaacagt agagaacaag 180
gagettgeta agaattaatt ttgetgtttt teaccecatt caaacagage tgeeetgtte 240
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cctgatggag ttccattcct gccagggcac ggctgagtaa cacgaagcca ttcaagaaag 300
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gcgctactta ataaatatat ttatactttg aaattatgat aaccgatttt tcccatgcgg 420
catcctaagg gcacttgcca gctcttatcc ggacagtcaa gcactgttgt tggacaacag 480
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<210> 129
<211> 521
<212> DNA
<213> Homo sapiens
<400> 129
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gaaagagagc cgggaaaggt catctctgtt agccagtcgc tacgattctc ccatcaactc 240
agetteacat attecateat etaaaactge ateteteect ggetatggaa gaaatggget 300
tcaccggcct gtttctaccg acttcgctca gtataacagc tatggggatg tcagcggggg 360
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<210> 130
<211> 270
<212> DNA
<213> Homo sapiens
<400> 130
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cttggtgaat acagteteet tecagaggte gggggteagg tagetgtagg tettagaaat 180
ggcatcaaag gtggccttgg cgaagttgcc cagggtggca gtgcagcccc gggctgaggt 240
gtagcagtca tcgataccag ccatcatgag
<210> 131
<211> 341
<212> DNA
<213> Homo sapiens
<400> 131
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ccagccattc gctcctactg atgagacaag atgtggtgat gacagaatca gcttttgtaa 120
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<211> 844
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 37
<223> n = A,T,C or G
<400> 132
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<210> 133 <211> 601 <212> DNA <213> Homo	sapiens		٠.			
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<210> 134 <211> 421 <212> DNA <213> Homo	sapiens					
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<210> 135 <211> 511 <212> DNA <213> Homo	sapiens					
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gaaactetta gaaggegaag aagagggtt gaagetgtet eeaageeett etteeegtgt 240
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<210> 136
<211> 341
<212> DNA
<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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                                                                551
<210> 138
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 490
<223> n = A, T, C or G
<400> 138
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ttgatttctc tttctcccaa tcggccccaa agagaccaca taaaaggaga gtacatttta 120
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tttcaaggan gcaggaaagc aattaagtgg tcaccttaac ataaggggga c
                                                                531
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<210> 139
<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 517
<223> n = A, T, C or G
<400> 139
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cacattgcag aagaggcaga taggaagtat gaagaggtgg ctcgtaagtt ggtgatcatt 420
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<210> 140
<211> 571
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 7
<223> n = A, T, C or G
<400> 140
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<210> 141
<211> 531
<212> DNA
<213> Homo sapiens
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tcagtccatt ccagttggca ccagcctgaa ccatttggta cctggtgtta actggagtcc 480
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<210> 142
<211> 491
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 410
<223> n = A, T, C or G
<400> 142
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atttgttgca agaaaccttg cccggatact agcggaaaac tggaggcggn ggtggggca 420
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<211> 515
<212> DNA
<213> Homo sapiens
<400> 143
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<210> 144
<211> 340
<212> DNA
<213> Homo sapiens
<400> 144
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cettetecae ggccacagte ceagecece caetecagte ettececaag gatgcageet 240
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<211> 630
<212> DNA
<213> Homo sapiens
<400> 145
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teeteaaaae gggetgagaa ggeeegteag gggeeeaggt eecacagaga ggeetgggat 180
actececeaa eeegaggge agaetgggea gtggggagee eeeategtge eeeaqaggtq 240
gccacagget gaaggagggg cctgaggcac cgcagcctgc aacccccagg gctgcagtcc 300
actaactttt tacagaataa aaggaacatg gggatgggga aaaaagcacc aggtcaggca 360
gggcccgagg gccccagatc ccaggagggc caggactcag gatgccagca ccaccctagc 420
ageteceaea geteetggea eaggaggeeg ceaeggattg geaeaggeeg etgetggeea 480
tcacgccaca tttggagaac ttgtcccgac agaggtcagc tcggaggagc tcctcgtggg 540
cacacactgt acgaacacag atctccttgt taatgacgta cacacggcgg aggctgcggg 600
gacagggcac gggaggtctc agccccactt
<210> 146
<211> 521
<212> DNA
<213> Homo sapiens
<400> 146
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atgacctgat ggattgctcg accaagacac agaagtgaag tctgtgtctg tgcacttccc 180
acagactgga gtttttggtg ctgaatagag ccagttgcta aaaaattggg ggtttggtga 240
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taatttattt tattctctct cctttttatt ttgcctgcag aatccgttga gagactaata 480
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                                                                   521
<210> 147
<211> 562
<212> DNA
<213> Homo sapiens
<400> 147
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gccgggttgg gacagcgtct tcgctgctgc tggatagtcg tgttttcggg gatcgaggat 120
actcaccaga aaccgaaaat gccgaaacca atcaatgtcc gagttaccac catggatgca 180
gagctggagt ttgcaatcca gccaaataca actggaaaac agctttttga tcaggtggta 240
aagactatcg gcctccggga agtgtggtac tttggcctcc actatgtgga taataaagga 300
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eccetecagt teaagtteeg ggeeaaagtt etaceetgaa gatgtggetg aggageteat 420
ccaggacatc acccagaaac ttttcttcct tcaagtgaag gaaggaatcc ttagcgatga 480
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tttggggact accaccaaga ag
                                                                  562
<210> 148
<211> 820
<212> DNA
<213> Homo sapiens
<400> 148
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gtctctggga caatctctag ggtcactacc tggaaactcg ttagggtaca actgaatgct 120
gaaaggaaag aacacctgca gaaccggaca gaaattcacc ccggcgatca gctgattgat 180
ctcggtcgac cagaagtcat ggctaaagat gacgaggacg ttgtcaattc cctgggcttt 240
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caccagetee eggggggeee aggtgeeage ettatetaca tteeteaggg tetgateaaa 360
gttcagctgg tacaccaggg accggtaccg cagcgtcagg ttgtccgctc gggctggggg 420
accgccggga ccagggaagc cgccgacacg ttggagaccc tgcggatgcc cacagccaca 480
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gaggggtggt ccccaccgcg gccgccggca ccccgcgcgg gttcggcgtc cagcaacggt 540
ggggcgaggg cctcgttctt cctttgtcgc ccattgctgc tccagaggac qaagccqcaq 600
gcggccacca cgagcgtcag gattagcacc ttccgtttgt agatgcggaa cctcatggtc 660
tecagggeeg ggagegeage tacagetega gegteggege egeegetagg ageegegget 720
eggettegte teegteetet eeatteagea eeaegggtee eggaaaaage teageesegg 780
tcccaaccgc accctagett cgttacctgc gcctcgcttg
<210> 149
<211> 501
<212> DNA
<213> Homo sapiens
<400> 149
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tgctcttcca gctgcatggc caggcgcaag gccttgatga catctcgcag ggctgagaaa 120
tgcttggctt gctgggccag agcagattcc gctttgttca caaaggtctc caggtcatag 180
tetggetget eggteatete agagagetea agecagtetg gteettgetg tatgatetee 240
ttgagetett ceatageett etecteeage teeetgatet gagteatgge ttegttaaag 300
ctggacatct gggaagacag ttcctcctct tccttggata aattgcctqq aatcaqcqcc 360
ccgttagagc aggcttccat ctcttctgtt tccatttgaa tcaactgctc tccactgggc 420
ccactgtggg ggctcagctc cttgaccctg ctgcatatct taagggtgtt taaaggatat 480
tcacaggage ttatgcctgg t
<210> 150
<211> 511
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 457, 479
<223> n = A, T, C or G
<400> 150
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gcattctgct ttgactttgc atttgatgaa acagcttcga atgaagttgt ctacaggttc 120
acagcaaggc cactggtaca gacaatcttt gaaggtggaa aagcaacttg ttttgcatat 180
ggccagacag gaagtggcaa gacacatact atgggcggag acctctctgg gaaagcccag 240
aatgcatcca aagggatcta tgccatggcc ttccgggacg tcttcttctg aagaatcaac 300
cctgctaccg gaagttgggc ctggaagtct atgtgacatt cttcgagatc tacaatggga 360
agetgtttga cetgeteaae aagaaggeea agettgegeg tgetggaaga eggeaageaa 420
caggtgcaag tggtgggggc ttgcaggaac atctggntaa ctctgcttga tgatggcant 480
caagatgatc gacatgggca gcgcctgcag a
                                                                   511
<210> 151
<211> 566
<212> DNA
<213> Homo sapiens
<400> 151
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caaatetttt gegeeaagat etgatgagae gaeaggaaga attaagaege atggaagaae 120
ttcacaatca agaaatgcag aaacgtaaag aaatgcaatt gaggcaagag gaggaacgac 180
gtagaagaga ggaagagatg atgattegte aaegtgagat ggaagaacaa atgaggegee 240
aaagagagga aagttacagc cgaatgggct acatggatcc acgggaaaga gacatgcgaa 300
tgggtggcgg aggagcaatg aacatgggag atccctatgg ttcaggaggc cagaaatttc 360
cacctctagg aggtggtggt ggcataggtt atgaagctaa tcctggcgtt ccaccagcaa 420
ccatgagtgg ttccatgatg ggaagtgaca tgcgtactga gcgctttggg cagggaggtg 480
```

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cggggcctgt gggtggacag ggtcctagag gaatggggcc tggaactcca gcaggatatg 540
gtagagggag agaagagtac gaaggc
<210> 152
<211> 518
<212> DNA
<213> Homo sapiens
<400> 152
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tgagaatgtc aaggcaaaga tccaagacaa ggaaggcatc cctcctgacc agcakaggtt 120
gatetttget gggaaacage tggaagatgg aegeaceetg tetgaetaca acatecagaa 180
agagtccacc etgcacctgg tgctccgtct cagaggtggg atgcaaatct tcgtgaaqac 240
cctgactggt aagaccatca ccctcgaggt ggagcccagt gacaccatcg agaatgtcaa 300
ggcaaagatc caagataagg aaggcatccc tcctgatcag cagaggttga tctttgctgg 360
gaaacagctg gaagatggac gcaccctgtc tgactacaac atccagaaag agtccactct 420
gcacttggtc ctgcgcttga gggggggtgt ctaagtttcc ccttttaagg tttcaacaaa 480
tttcattgca ctttcctttc aataaagttg ttgcattc
<210> 153
<211> 542
<212> DNA
<213> Homo sapiens
<400> 153
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tctgctctga gcctccttgt cgcctgcatt tagatggctc ccgcaaagaa gggtggcgag 180
aagaaaaagg gccgttctgc catcaacgaa gtggtaaccc gagaatacac catcaacatt 240
cacaagcgca tccatggagt gggcttcaag aagcgtgcac ctcgggcact caaagagatt 300
cggaaatttg ccatgaagga gatgggaact ccagatgtgc gcattgacac caggctcaac 360
aaagctgtct gggccaaagg aataaggaat gtgccatacc gaatccgtgt gcggctgtcc 420
agaaaacgta atgaggatga agattcacca aataagctat atactttggt tacctatgta 480
cctgttacca ctttcaaaaa tctacagaca gtcaatgtgg atgagaacta atcgctgatc 540
gt
<210> 154
<211> 411
<212> DNA
<213> Homo sapiens
<400> 154
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ctecetetee ateceeteae eccaeceett agecaeagtg aagggaatgg aaaatgagaa 120
gccacgaggg cccctgccag ggaaggctgc cccagatgtg tggtgagcac agtcagtgca 180
gctgtggctg gggcagcagc tgccacaggc tcctccctat aaattaagtt cctgcagcca 240
cagctgtggg agaagcatac ttgtagaagc aaggccagtc cagcatcaga aggcagagc 300
ageateagtg acteceagee atggaatgaa eggaggacae agageteaga gacagaacag 360
gccaggggga agaaggagag acagaatagg ccagggcatg gcggtgaggg a
<210> 155
<211> 421
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 173
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<223> n = A, T, C or G
<400> 155
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actggttccc taagaaatcc aaggagaatc ctcggaactt ctcggataac cagctgcaag 120
agggcaagaa cgtgatcggg ttacagatgg gcaccaaccg cggggcgtct cangcaggca 180
tgactggcta cgggatgcca cgccagatcc tctgatccca ccccaggcct tgcccctgcc 240
ctcccacgaa tggttaatat atatgtagat atatatttta gcagtgacat tcccagagag 300
ccccagaget ctcaagetee tttctgtcag ggtggggggt tcaagectgt cctgtcacct 360
ctgaagtgcc tgctggcatc ctctcccca tgcttactaa tacattccct tccccatagc 420
<210> 156
<211> 670
<212> DNA
<213> Homo sapiens
<400> 156
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aactccagcg actgggtaac cactgacatt caggtgaagg tgcgggacac ctacctggat 120
acacaggtgg tgggacagac aggtgtcatc cgcagtgtca cggggggcat gtgctctgtg 180
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cccaccaaga acaacaaggt gaaagtgatc ctgggcgagg atcgggaagc cacgggcgtc 300
ctactgagca ttgatggtga ggatggcatt gtccgtatgg accttgatga gcagctcaag 360
atcetcaace teegetteet ggggaagete etggaageet gaageaggea gggeeggtgg 420
acttcgtcgg atgaagagtg atcctccttc cttccctggc ccttggctgt gacacaagat 480
cctcctgcag ggctaggcgg attgttctgg atttcctttt gtttttcctt ttaggtttcc 540
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ttcctgtacc tcctccccac agcttgcttt tgttgtaccg tctttcaata aaaagaagct 660
gtttggtcta
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<210> 157
<211> 421
<212> DNA
<213> Homo sapiens
<400> 157
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aagaatcgag ttgaaatcaa tgatgtggag cctgaagttt ttaaggaaat gatgtgcttc 180
atttacacgg ggaaggetee aaacetegae aaaatggetg atgatttget ggeagetget 240
gacaagtatg ccctggagcg cttaaaggtc atgtgtgagg atgccctctg cagtaacctg 300
tccgtggaga acgctgcaga aattctcatc ctggccgacc tccacagtgc agatcagttg 360
aaaactcagg cagtggattt catcaactat catgcttcgg atgtcttgga gacctcttgg 420
Œ
<210> 158
<211> 321
<212> DNA
<213> Homo sapiens
<400> 158
tegtagecat ttttetgett etttggagaa tgaegecaea etgaetgete attgtegttg 60
gttccatgcc aattggtgaa atagaacctc atccggtagt ggagccggag ggacatcttg 120
tcatcaacgg tgatggtgcg atttggagca taccagagct tggtgttctc gccatacagg 180
gcaaagaggt tgtgacaaag aggagagata cggcatgcct gtgcagccct gatgcacagt 240
teetetgetg tgtactetee aetgeecage eggagggget eeetgteega eagatagaag 300
atcacttcca cccctggctt g
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```
<210> 159
<211> 596
<212> DNA
<213> Homo sapiens
<400> 159
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cttttgagtg gtaatcatat gtgtctttat agatgtacat acctccttgc acaaatggag 120
gggaattcat tttcatcact gggagtgtcc ttagtgtata aaaaccatgc tggtatatgg 180
cttcaagttg taaaaatgaa agtgacttta aaagaaaata ggggatggtc caggatctcc 240
actgataaga ctgtttttaa gtaacttaag gacctttggg tctacaagta tatgtgaaaa 300
aaatgagact tactgggtga ggaaattcat tgtttaaaga tggtcgtgtg tgtgtgtgtg 360
ttgaaattac tgkgtaaata tatgtytgat aatgatttgc tytttgvcma ctaaaattag 480
gwctgtataa gtwctaratg cmtccctggg kgttgatytt ccmagatatt gatgatamcc 540
cttaaaattg taaccygcct ttttcccttt gctytcmatt aaagtctatt cmaaag
<210> 160
<211> 515
<212> DNA
<213> Homo sapiens
<400> 160
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cagtgtcaga ggcccgcgtt cagcccaaga atgtggattt tctctcccta ttgatcacag 120
tgggtgggtt tcttcagaaa agccccagag gcagggacca gtgagctcca aggttagaag 180
tggaactgga aggetteagt cacatgetge ttecaegett ceaggetggg cageaaggag 240
gagatgccca tgacgtgcca ggtctcccca tctgacacca gtgaagtctg gtaggacagc 300
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gtetgagtee ggaataggag caggggcagg teeetgegga gaggeaette tggeetgaag 420
acageteeat tgageceetg eagtacaggy gtagtgeett ggaceaagee eacageetgg 480
taaggggcgc ctgccagggc cacggccagg aggca
<210> 161
<211> 936
<212> DNA
<213> Homo sapiens
<400> 161
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accaegecea egtecacete gtecteceet geegecaegt eetgggegge caaggtetee 240
aaaattgatc tccagctgag acgttatatc atttgctggc ttccggaaat gatggtccat 300
aaccgaatct tcagcatgag cetetteaet etttgattta tgaagaacaa atecettett 360
ccactgccca tcagcacctt catttggttt tcggatatta aattctactt ttgcccggtc 420
cttattttga atagcettee acteateeaa agteatetet tttggaeeet eetetttae 480
ctcttcaact tcattctcct tattttcagt gtctgccact ggatgatgtt cttcaccttc 540
aggtgtttcc tcagtcacat ttgattgatc caagtcagtt aattcgtctt tgacagttcc 600
ccagttgtga gatccgctac ctccacgttt gtcctcgtgc ttcaggccag atctatcact 660
tecaetatge etateaaatt caegtttgee acgagaatea aatecatete eteggeeeat 720
tecaegteca eggeeeete gaeetettee aagaeeaeea egaeetegaa taggteggte 780
aataatcggt ctatcaactg aaaattcgcc tccttcaccc ttttcttcaa gtggcttttc 840
gaatcttcgt tcacgaggtg gtcgcctttc tggtcttcta tcaattattt tcccttcacc 900
ctgaagttgt tgatcaggtc ttcttccaac tcgtgc
```

```
<211> 950
<212> DNA
<213> Homo sapiens
<400> 162
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cgacatcagt gacagacgga agcagcagac catcaaggct acgggaggcc cggggcgctt 120
gcgaagatga agtttggctg cctctccttc cggcagcctt atqctqqctt tqtcttaaat 180
ggaatcaaga ctgtggagac gcgctggcgt cctctgctga gcagccagcg gaactgtacc 240
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gagagactcg ggatgactcc tgctcagatt caggccttgc tcaggaaagg ggaaaagttt 360
ggtcgaggag tgatagcggg actcgttgac attggggaaa ctttgcaatg ccccgaagac 420
ttaactcccg atgaggttgt ggaactagaa aatcaagctg cactgaccaa cctgaagcag 480
aagtacctga ctgtgatttc aaaccccagg tggttactgg agcccatacc taggaaagga 540
ggcaaggatg tattccaggt agacatccca gagcacctga tccctttggg gcatgaagtg 600
tgacaagtgt gggctcctga aaggaatgtt ccrgagaaac cagctaaatc atggcacctt 660
caatttgcca tcgtgacgca gacctgtata aattaggtta aagatgaatt tccactgctt 720
tggagagtcc cacccactaa gcactgtgca tgtaaacagg ttcctttgct cagatgaagg 780
aagtaggggg tggggctttc cttgtgtgat gcctccttag gcacacaggc aatgtctcaa 840
gtactttgac cttagggtag aaggcaaagc tgccagtaaa tgtctcagca ttgctqctaa 900
ttttggtcct gctagtttct ggattgtaca aataaatgtg ttgtagatga
<210> 163
<211> 475
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 301, 317, 331, 458, 464, 470
<223> n = A, T, C or G
<400> 163
tegageggee geeegggeag gtgteggagt ceageaeggg aggegtggte ttgtagttgt 60
teteeggetg eccattgete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
acacetgtgg ttetegggge tgecetttgg etttggagat ggtttteteg atgqqqqetq 240
ggagggcttt gttggagacc ttgcacttgt actccttqcc attcaaccag tcctqqtqca 300
ngacggtgag gacgctnacc acacggtacg ngctggtgta ctqctcctcc cgcqqctttq 360
tcttggcatt atgcacctcc acgccgtcca cgtaccaatt gaacttgacc tcagggtctt 420
cgtggctcac gtccaccacc acgcatgtaa cctcaaanct cggncgcgan cacgc
<210> 164
<211> 476
<212> DNA
<213> Homo sapiens
<400> 164
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ecetgaggte aagtteaact ggtaegtgga eggegtggag gtgeataatg ceaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
cctgcccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct gcctggtcaa 360
aggettetat eccagegaca tegecegtgg agtgggagag caatgggeag eeggagaaca 420
actacaagac cacgcctccc gtgctggact ccgacacctg ccgggcgqcc gctcga
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<210> 165

```
<211> 256
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 10, \overline{3}7, 249
\langle 223 \rangle n = A, T, C or G
<400> 165
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gcaacatgga gactggtgag acctgcgtgt accccactca gcccagtgtg gcccagaaga 120
actggtacat cagcaagaac cccaaggaca agaggcatgt ctggttcggc gagagcatga 180
ccgatggatt ccagttcgag tatggcggcc agggctccga ccctgccgat gtggacctgc 240
ccgggcggnc gctcga
<210> 166
<211> 332
<212> DNA
<213> Homo sapiens
<400> 166
agcgtggtcg cggccgaggt caagaacccc gcccgcacct gccgtgacct caagatgtgc 60
cactetgact ggaagagtgg agagtactgg attgacccca accaaggetg caacetggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
gccgatgtgg acctgcccgg gcggccgctc ga
<210> 167
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 77, 109, 136, 184, 198
<223> n = A, T, C or G
<400> 167
tegageggte geeegggeag gtecacateg geagggtegg agecetggee geeatacteg 60
aactggaatc catcggncat gctctcgccg aaccagacat gcctcttgnc cttggggttc 120
ttgctgatgt accagntctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccantctcca tgttgcanaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact etccaetett ecagacagag tggcacatet tgaggteacg gcaggtgegg 300
gcggggttct tgacctcggt cgcgaccacg ct
<210> 168
<211> 276
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 72, 84
<223> n = A, T, C or G
<400> 168
```

```
tegageggee geeegggeag gteeteetea gageggtage tqttettatt geeeeggeag 60
cctccataga tnaagttatt gcangagttc ctctccacgt caaagtacca gcgtgggaag 120
gatgcacggc aaggcccagt gactgcgttg gcggtgcagt attcttcata gttgaacata 180
tcgctggagt ggacttcaga atcctgcctt ctgggagcac ttgggacaga ggaatccgct 240
gcattectgc tggtggacct cggccgcgac cacgct
<210> 169
<211> 276
<212> DNA
<213> Homo sapiens
<400> 169
agegtggteg eggeegaggt ceaceageag gaatgeageg gatteetetg teceaagtge 60
tcccagaagg caggattctg aagaccactc cagcgatatg ttcaactatg aagaatactg 120
caccgccaac gcagtcactg ggccttgccg tgcatccttc ccacgctggt actttgacgt 180
ggagaggaac teetgeaata actteateta tggaggetge eggggeaata agaacageta 240
ccgctctgag gaggacctgc ccgggcggcc gctcga
<210> 170
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 294
<223> n = A,T,C or G
<400> 170
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagccagaa tggcacatct tgaggtcacg gcangtgcgg 300
geggggttet tgacetegge egegaceaeg et
<210> 171
<211> 333
<212> DNA
<213> Homo sapiens
<400> 171
agcgtggtcg cggccgaggt caagaaaccc cgcccgcacc tgccgtgacc tcaagatgtg 60
ccactctggc tggaagagtg gagagtactg gattgacccc aaccaaggct gcaacctgga 120
tgccatcaaa gtcttctgca acatggagac tggtgagacc tgcgtgtacc ccactcagcc 180
cagtgtggcc cagaagaact ggtacatcag caagaacccc aaggacaaga ggcatgtctg 240
gctcggcgag agcatgaccg atggattcca gttcgagtat ggcggccagg gctccgaccc 300
tgccgatgtg gacctgcccg ggcggccgct cga
                                                                   333
<210> 172
<211> 527
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 46, 125, 140, 148, 220, 229, 291, 388, 456
<223> n = A, T, C or G
```

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<400> 172
agegtggteg eggeegaggt cetqteagag tggcactggt agaagnteea ggaaccetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cetgnaatgg ggcccatgan atggttgnct gagagagagc ttettgtcct acatteggeg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgn gggcggtgng gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca naagtgccag 300
gaagetgaat accattteea gtgteataee cagggtgggt gaegaaaggg gtettttgaa 360
ctgtggaagg aacatccaag atctctgntc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgctgtct ttttccttcc aatcangggc tcgctcttct qaatattctt 480
cagggcaatg acataaattg tatattcggt tcccggttcc aggccag
<210> 173
<211> 635
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 444, 453, 517, 540, 546, 551, 573, 593
<223> n = A, T, C or G
<400> 173
tegageggee geeegggeag gtecaccaca eccaatteet tgetggtate atggeageeq 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactqq cctgqaaccq 180
ggaaccgaat atacaattta tgtcattgcc ctgaaqaata atcagaaqag cqagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgangaacat ggntttagge ggaccacace ggccacaacg 480
ggcaccccca taaggcatag gccaagaaca tacccgncga atgtaggaca agaagctctn 540
tctcanacaa ncatctcatg ggccccattc cangacactt ctgagtacat canttcatgg 600
catcctggtg gcactgataa aaacccttac agtta
<210> 174
<211> 572
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 457, 511, 520, 552, 568
<223> n = A, T, C or G
<400> 174
agcgtggtcg cgggcgaggt cctgtcagag tggcactggt agaagttcca ggaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca qaaqtgccaq 300
gaagetgaat accattteea gtgteatace cagggtgggt gacgaaaggg gtettttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcanggg ctcgctctc tgattattct 480
tcagggcaat gacataaatt gtatattcgg ntcccgggtn cagccaataa taataaccct 540
ctgtgacacc anggcggggc cgaagganca ct
```

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<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 247
<223> n = A, T, C or G
<400> 175
agcgtggtcg cggccgaggt cctcaccaga ggtaccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac agtttcccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gacgtcagg gagaaaatgg acctgcccgg 360
gcggccgctc ga
<210> 176
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 251
<223> n = A, T, C or G
<400> 176
togagoggco gocogggcag gtocattttc tocotgacgg toccacttct ctocaatctt 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ntgacagagt tgeccaeggt aacaacetet teeggaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggta cctctggtga ggacctcggc 360
cgcgaccacg ct
                                                                   372
<210> 177
<211> 269
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222>94, \overline{2}25
<223> n = A, T, C or G
<400> 177
agcgtggccg cggccgaggt ccattggctg gaacggcatc aacttggaag ccaqtgatcg 60
teteageett ggtteteeag etaatggtga tggnggtete agtageatet gteacacqaq 120
cccttcttgg tgggctgaca ttctccagag tggtgacaac accctgagct ggtctgcttg 180
tcaaagtgtc cttaagagca tagacactca cttcatattt ggcgnccacc ataagtcctg 240
atacaaccac ggaatgacct gtcaggaac
                                                                   269
<210> 178
<211> 529
<212> DNA
<213> Homo sapiens
```

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<400> 178
tegageggee geeegggeag gteeteagae egggttetga gtacacagte agtgtggttq 60
ccttgcacga tgatatggag agccagccc tgattggaac ccagtccaca gctattcctg 120
caccaactga cctgaagttc actcaqqtca caccacaaq cctqaqcqcc caqtqqacac 180
cacccaatgt teageteact ggatategag tgeggqtqac ceccaaggag aagaceggac 240
caatqaaaga aatcaacctt gctcctgaca gctcatccgt ggttgtatca ggacttatgg 300
cggccaccaa atatgaagtg agtgtctatg ctcttaagga cactttgaca agcaqaccag 360
ctcagggtgt tgtcaccact ctggagaatg tcagcccacc aagaagggct cqtqtgacaq 420
atgetactga gaccaccatc accattaget ggagaaccaa gactgagacg atcactgget 480
tccaagttga tgccgttcca gccaatggac ctcggccgcg accacgctt
<210> 179
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 64
<223> n = A, T, C or G
<400> 179
agcgtggtcg cggccgaggt ctggccgaac tgccagtgta cagggaagat gtacatgtta 60
tagnitettet egaagteeeg ggeeageage teeaeggggt ggteteetge eteeaggege 120
tteteattet catggatett etteaceege agettetget teteagteag aaggttgttg 180
tecteatece teteatacag ggtgaccagg acgttettga gecagteceg catgegeagg 240
gggaattegg teageteaga gteeaggeaa ggggggatgt atttqeaagg eecgatgtag 300
tocaagtgga gottgtggcc cttottggtg coctocaagg tgcactttgt ggcaaagaag 360
tggcaggaag agtcgaaggt cttqttqtca ttqctqcaca ccttctcaaa ctcqccaatq 420
ggggctgggc agacctgccc gggcggccgc tcga
<210> 180
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature . <222> 55, 299, 317, 332, 342, 348
<223> n = A, T, C or G
<400> 180
tegageggee geeegggeag gtetgeeeag ceeceattgg egagtttgag aaggngtgea 60
gcaatgacaa caagaccttc gactcttect gccacttett tgccacaaaq tgcacctqq 120
agggcaccaa gaagggccac aagctccacc tggactacat cgggccttgc aaatacatcc 180
ccccttgcct ggactctgag ctgaccgaat tccccctgcg catgcgggac tggctcaaga 240
acgtcctggt caccctgtat gagagggatg aggacaacaa ccttctgact gagaagcana 300
agctgcgggt gaagaanatc catgagaatg anaagcgcct gnaggcanga gaccaccccg 360
tggagetget ggeeegggae ttegagaaga actataacat gtacatette cetgtacaet 420
ggcagttcgg ccagacctcg gccgcgacca cgct
<210> 181
<211> 102
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 8, 47, 60, 67
<223> n = A, T, C or G
<400> 181
agegtggntg eggacgacgc ecacaaagcc attgtatgta gttttantte agetgcaaan 60
aataccncca gcatccacct tactaaccag catatgcaga ca
<210> 182
<211> 337
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 169, 195, 253, 314
<223> n = A, T, C or G
<400> 182
tcgagcggtc gcccgggcag gtctgggcgg atagcaccgg gcatattttg gaatggatga 60
ggtctggcac cctgagcagc ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggtt ctgagtctgt gggatagctg ccatgaagna acctgaaqqa 180
ggegetggct ggtangggtt gattacaggg ctgggaacag ctcgtacact tgccattctc 240
tgcatatact ggntagtgag gcgagcctgg cgctcttctt tgcgctgagc taaagctaca 300
tacaatggct ttgnggacct cggccgcgac cacgctt
<210> 183
<211> 374
<212> DNA
<213> Homo sapiens
togageggee geoegggeag gtecatttte teeetgaegg teeeacttet etecaatett 60
gtagttcaca ccattgtcat gacaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tecaaeggea taatgggaaa etgtgtaggg qteaaaqeae qaqteateeq taqqttqqtt 240
caageetteg ttgacagaag ttgeceaegg taacaacete tteeegaace ttatgeetet 300
gctggtcttt caagtgcctc cactatgatg ttgtaggtgg cacctctggt gaggacctcg 360
gccgcgacca cgct
<210> 184
<211> 375
<212> DNA ·
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30, 174, 248, 285, 306, 332, 345, 368
<223> n = A, T, C or G
<400> 184
agcgtggttt gcggccgagg tcctcaccan aggtgccacc tacaacatca tagtggaggc 60
actgaaagac cagcagaggc ataaggttcg ggaagaggtt gttaccgtgg gcaactctgt 120
caacgaaggc ttgaaccaac ctacggatga ctcgtgcttt gacccctaca cagnttccca 180
ttatgccgtt ggagatgagt gggaacgaat gtctgaatca ggctttaaac tgttgtgcca 240
gtgcttangc tttggaagtg gtcatttcag atgtgattca tctanatggt gtcatgacaa 300
tggtgngaac tacaagattg gagagaagtg gnaccgtcag ggganaaaat ggacctgccc 360-
gggcggcncg ctcga
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<210> 185
<211> 148
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 28, 36, 86
<223> n = A, T, C or G
<400> 185
agcqtqqtcq cqqccqaqqt ctqqcttnct qctcanqtqa ttatcctqaa ccatccaggc 60
caaataagcg ccggctatgc ccctgnattg gattgccaca cggctcacat tgcatgcaag 120
tttgctgagc tgaaggaaaa gattgatc
<210> 186
<211> 397
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 78
<223> n = A, T, C or G
<400> 186
tegageggee geeegggeag gtecaattga aacaaacagt tetgagaceg ttettecace 60
actgattaag agtggggngg cgggtattag ggataatatt catttagcct tctgagcttt 120
ctgggcagac ttggtgacet tgccagetec ageageette tggtccactg etttgatgac 180
acceacegea actgtctgtc teatateaeg aacageaaag egaceeaaag gtggatagtc 240
tgagaagete teaacacaca tgggettgee aggaaccata teaacaatgg geageateac 300
cagacttcaa gaatttaagg gccatcttcc agctttttac cagaacggcg atcaatcttt 360
teetteaget cageaaaett geatgeaatg tgageeg
                                                                   397
<210> 187
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 145, 286, 363, 365, 425, 433, 452, 462, 471, 512, 514, 534,
536, 540, 565, 583
<223> n = A, T, C or G
<400> 187
tegageggee geeegggeag gteeagaggg etgtgetgaa gtttgetget geeactggag 60
ccactccaat tgctggccgc ttcactcctg gaaccttcac taaccagatc caggcagcct 120
teegggagee aeggettett gtggntaetg aeeceaggge tgaceaeeag eeteteaegg 180
aggeatetta tgttaaceta cetaceattg egetgtgtaa cacagattet cetetgeget 240
atgtggacat tgccatccca tgcaacaaca agggagctca ctcagngggg tttgatgtgg 300
tggatgctgg ctcgggaagt tctgcgcatg cgtggcacca tttcccgtga acacccatgg 360
gangneatge etgatetgga ettetacaga gateetgaag agattgaaaa agaagaacag 420
gctgnttgct ganaaagcaa gtgaccaagg angaaatttc angggtgaaa nggactgctc 480
ccgctcctga attcactgct actcaacctg angntgcaga ctggtcttga aggngnacan 540
gggccctctg ggcctattta agcancttcg gtcgcgaaca cgnt
```

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<210> 188
<211> 579
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 136, 486
<223> n = A, T, C or G
<400> 188
agegtgngtc geggeegagg tgctgaatag geacagaggg caectgtaca cettcagace 60
agtetgeaac eteaggetga gtageagtga aeteaggage gggageagte eatteaceet 120
gaaatteete ettggneaet geetteteag eageageetg etettettt teaatetett 180
caggatetet gtagaagtac agateaggea tgacetecca tgggtgttea egggaaatgg 240
tgccacgcat gcgcagaact tcccgagcca gcatccacca catcaaaccc actgagtgag 300
ctcccttgtt gttgcatggg atgggcaatg tccacatagc gcagaggaga atctgtgtta 360
cacagegeaa tggtaggtag gttaacataa gatgeeteeg egagaagetg gtggteagee 420
ctggggtcaa gtaaccacaa gaagccgtgg ctcccggaag gctgcctgga tctqgttagt 480
gaaggntcca ggagtgaagc ggccaacaat tggagtggct tcagtggcaa gcagcaaact 540
tcagcacaag ccctctggac ctgcccggcg gccgctcga
<210> 189
<211> 374
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 41, \overline{2}80, 314, 330, 350, 353
<223> n = A, T, C or G
<400> 189
tegageggee geeegggeag gtecatttte teeetgaegg neceaettet etceaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caagectteg ttgacagagt tgcccacggt aacaaceten teccegaace ttatgeetet 300
getgggettt cagngcetce actatgatgn tgtagggggg cacetetggn gangaceteg 360
geegegaeea eget
<210> 190
<211> 373
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247, 304, 306, 332, 337
<223> n = A, T, C or G
<400> 190
agcgtggtcg cggccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggctcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaagget tgaaccaacc tacggatgac tegtgetttg accectacac agttteccat 180
tatgccqttq qaqatqaqtq qqaacqaatq tctqaatcaq qctttaaact qttqtqccaq 240
tgcttangct ttggaagtgg gtcatttcag atgtgattca tctagatggt gccatgacaa 300
tggngngaac tacaagattg gagagaagtg gnaccqncag ggagaaaatg gacctqcccg 360
```

```
ggcggccgct cga
                                                                   373
<210> 191
<211> 354
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 218, 299, 306, 326, 333, 337, 341
<223> n = A, T, C or G
<400> 191
agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtctccatg ttgcagaaga ctttgatggc atccaggntg caaccttggt tggggtcaat 240
ccagtactet ccactettee agecagagtg geacatettg aggteaegge aggtgeggne 300
gggggntttt gcggctgccc tctggncttc ggntgtnctc natctgctgg ctca
<210> 192
<211> 587
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 276
<223> n = A,T,C or G
<400> 192
tegageggee geeegggeag gtetegeggt egeactggtg atgetggtee tgttggteec 60
cceggccete ctggacetec tggcccccet ggtcctccca gcgctggttt cgacttcagc 120
ttectgeece agecacetea agagaagget cacgatggtg geegetacta eegggetgat 180
gatgccaatg tqqttcqtqa ccqtqacctc qaqqtqqaca ccaccctcaa qaqcctqaqc 240
cagcagateg agaacateeg gageecagag ggeagnegea agaaceeege eegeacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caagetgeaa cetggatgee ateaaagtet tetgeaacat ggagaetggt gagaeetgeg 420
tgtaccccac tcagcccagt gtggcccaaa agaactggta catcagcaag aaccccaagg 480
acaagaagca tgtctggttc ggcgagaaca tgaccgatgg attccagttc gagtatggcg 540
ggcagggetc cgaccctgcc gatggggacc ttggccgcga acacgct
<210> 193
<211> 98
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 33, 58, 71, 90
<223> n = A, T, C or G
<400> 193
agcgtggnng cggccgaggt ataaatatcc agnccatatc ctccctccac acgctganag 60
atgaagctgt ncaaagatct cagggtggan aaaaccat
<210> 194
<211> 240
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<212> DNA
<213> Homo sapiens .
<400> 194
togagoggco geologgcag gtoottoaga ottggactgt gtoacactgc caggottoca 60
gggctccaac ttgcagacgg cctgttgtgg gacagtctct gtaatcgcga aagcaaccat 120
qqaaqacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
ctctcagcgt gcggagggag gctctggact ggatatttct acctcggccg cgaccacgct 240
<210> 195
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 22, 37, 39, 105, 268, 276, 302, 323, 331, 335, 347, 351,
371, 378
<223> n = A, T, C or G
<400> 195
cgagcgggcg accgggcagg tncagactcc aatccanana accatcaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aaganctacc tgcacacctt 120
gaatgacaat geteggaget eeeetgtggt eategaegee teeactgeea ttgatgeace 180
atccaacctg cgtttcctgg ccaccacacc caattccttg ctggtatcat ggcagccgcc 240
acgtgccagg attaccggta catcatcnag tatganaagc ctgggcctcc tcccagagaa 300
gnggtccctc ggccccgccc tgntgtccca naggntacta ttactgngcc ngcaaccggc 360
aaccgatate nattttgnca ttggccttca acaataatta
<210> 196
<211> 494
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 19, 83, 168, 252, 271, 292, 430
<223> n = A, T, C or G
<400> 196
agegtggttc geggeegang teetgteaga gtggeactgg tagaagttee aggaaceetg 60
aactgtaagg gttcttcatc agngccaaca ggatgacatg aaatgatgta ctcagaagtg 120
tectggaatg gggeecatga gatggttgte tgagagagag ettettgnee tgtettttte 180
cttccaatca ggggctcgct cttctgatta ttcttcaggg caatgacata aattgtatat 240
tegggteeeg gnteeaggee agtaatagta neetetgtga caccagggeg gngeegaggg 300
accacttctc tgggaggaga cccaggcttc tcatacttga tgatgtaacc ggtaatcctg 360
qcacqtqqcq qctqccatqa taccaqcaaq qaattqqqt qtqqtqqcca qqaaacqcaq 420
gttggatggn gcatcaatgg cagtggaggc cgtcgatgac cacaggggga gctccgacat 480
tgtcattcaa ggtg
<210> 197
<211> 118
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
```

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<222> 8, 71, 96
<223> n = A, T, C or G
<400> 197
agegtggneg eggeegaggt geagegeggg etgtgeeace ttetgetete tgeecaaega 60
taaggagggt neetgeeece aggagaacat taactnteec cageteggee tetgeegg
<210> 198
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 41, 53, 98, 195, 350
<223> n = A, T, C or G
<400> 198
tcgagcggcc gcccgggcag gttttttttg ctgaaagtgg ntactttatt ggntgggaaa 60
gggagaaget gtggtcagec caagagggaa tacagagnee egaaaaaggg gagggcaggt 120
gggetggaac cagacgcagg gccaggcaga aactttetet ceteaetget cageetggtg 180
gtggctggag ctcanaaatt gggagtgaca caggacacct tcccacagcc attgcggcgg 240
catttcatct ggccaggaca ctggctgtcc acctggcact ggtcccgaca gaagcccgag 300
ctggggaaag ttaatgttca cctgggggca ggaaccctcc ttatcattgn gcagagagca 360
gaaggtggca cageeegege tgeacetegg eegegaeeae get
                                                                   403
<210> 199
<211> 167
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 92, 107
<223> n = A, T, C or G
<400> 199
tcgagcggcc gcccgggcag gtccaccata agtcctgata caaccacgga tgagctgtca 60
ggagcaaggt tgatttettt cattggteeg gnetteteet tgggggneac cegeactega 120
tatccagtga gctgaacatt gggtggcgtc cactgggcgc tcaggct
<210> 200
<211> 252
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 210, 226, 227, 230, 236
<223> n = A,T,C or G
<400> 200
tegageggtt egeeegggea ggteeaceac acceaattee ttgetggtat catggeagec 60
gccacqtqcc aggattaccq qctacatcat caaqtatqaq aagcctqqqt ctcctcccaq 120
agaageggte ceteggeece qeeetggtgt cacagagget actattactg geetggaace 180
qqqaaccqaa tatacaattt atqtcattqn cctqaaqaat aatcannaan aqcqancccc 240
tgattggaag ga
                                                                   252
```

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<210> 201
<211> 91
<212> DNA
<213> Homo sapiens
<400> 201
ttttttttt tttttttt ttttttt t
<210> 202
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 9, 354
<223> n = A, T, C or G
<400> 202
tegageggne geeegggeag gtetgeeaac accaagattg geeeeggeg catecacaca 60
gtccgtgtgc ggggaggtaa caagaaatac cgtgccctga ggttggacgt ggggaatttc 120
tcctggggct cagagtgttg tactcgtaaa acaaggatca tcgatgttgt ctacaatgca 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatcgac 240
agcacaccgt accgacagtg gtacgagtcc cactatgcgc tgcccctggg ccgcaagaag 300
ggagccaagc tgactcctga ggaagaagag attttaaaca aaaaacgatc taanaaaaaa 360
aaaacaat
<210> 203
<211> 340
<212> DNA
<213> Homo sapiens
<400> 203
agegtggteg eggeegaggt gaaatggtat teagetteet ggeaettetg gteageaace 60
cagtgttggg caacaaatga tctttgagga acatggtttt aggcggacca caccgcccac 120
aacggccacc cccataaggc ataggccaag accatacccg ccgaatgtag gacaagaagc 180
teteteteag acaaccatet catgggeece attecaggae acttetgagt acateattte 240
atgtcatcct gttggcactg atgaagaacc cttacagttc agggttcctq gaacttctac 300
cagtgccact ctgacaggac ctgcccgggc ggccgctcga
<210> 204
<211> 341
<212> DNA
<213> Homo sapiens
<400> 204
tegageggee geeegggeag gteetgteag agtggeactg gtagaagtte caggaaccet 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcaqaaqt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
egggtatggt ettggeetat geettatggg ggtggeegtt gtgggeggtg tggteegeet 240
aaaaccatgt teetcaaaga teattigtig eccaacactg ggtigetgac cagaagtgee 300
aggaagetga ataccattte aceteggeeg egaceaeget a
<210> 205
<211> 770
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 529, 591, 623, 626, 629, 630, 656, 702, 709, 712, 717, 743,
746, 749, 759, 762, 766
<223> n = A, T, C or G
<400> 205
tegageggee geeegggeag gteteeette ttgeggeeea qqqqeaqeqe ataqtqqqae 60
tegtaceact gteggtacgg tgtgctgteg atgageacga tgcaattett caccagggte 120
ttggtacgaa ccagctcgtt attagatgca ttgtagacaa catcgatgat ccttgtttta 180
cgagtacaac actctgagcc ccaggagaaa ttccccacgt ccaacctcag ggcacggtat 240
ttettgttac eteceegeae aeggaetgtg tggatgegge gggggeeaag etgaeteetg 300
aggaagaaga gattttaaac aaaaaacgat ctaaaaaaat tcagaagaaa tatgatgaaa 360
ggaaaaagaa tgccaaaatc agcagtctcc tggaggagca gttccagcag ggcaagcttc 420
ttgcgtgcat cgcttcaagg ccgggacagt gtgaccgagc agatggctat gtgctagagg 480
gcaaagaagt ggagttctat cttaagaaaa tcagggccca gaatggtgng tcttcaacta 540
atccaaaggg gagtttcaga ccagtgcaat cagcaaaaac attgatactg ntggccaaat 600
ttattggtgc agggcttgca cantangann ggctgggtct tggggcttgg attggnacaa 660
gctttggcag ccttttcttt ggttttgcca aaaacctttt gntgaagang anacctnggg 720
cggacccctt aaccgattcc acnccnggng gcgttctang gncccncttg
<210> 206
<211> 810
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 574, 621, 625, 636, 668, 673, 704, 728, 743, 767, 772, 786,
789, 807, 809, 810
<223> n = A, T, C or G
<400> 206
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aggetgecaa agaetgttee aataceagea eeagaaceag eeacteetae tgttgeagea 120
cctgcaccaa taaatttggc agcagtatca atgtctctgc tgattgcact ggtctgaaac 180
tccctttgga ttagctgaga cacaccattc tgggccctga ttttcctaag atagaactcc 240
aactetttge cetetageae atageeatet geteggteae aetgteeegg cettgaageg 300
atgeaegeaa gaagettgee etgetggaae tgeteeteea ggagaetget gattttggea 360
ttctttttcc tttcatcata tttcttctga atttttttag atcgttttt gtttaaaatc 420
tettetteet caggagteag ettggeecce geegeateca caeagteegt gtgegggag 480
gtaacaagaa ataccgtgcc ctgaggttgg acgtggggaa tttctcctgg ggctcagagt 540
ggtgtactcg taaaacaagg atcatcgatg gtgnctacaa tgcatctaat aacqagctqq 600
gtcqgaccca aagaacctgg ngaanaaatg gatcgnctca tcgacaggac accgtacccg 660
acaqqqqnac gantcccact atgcgcttgc ccctgggccg caanaaagga aaactgcccg 720
ggcggccntc gaaagcccaa ttntggaaaa aatccatcac actgggnggc cngtcgagca 780
tgcatntana ggggcccatt ccccctnann
                                                                  810
<210> 207
<211> 257
<212> DNA
<213> Homo sapiens
<400> 207
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tetgeaacat ggagaetggt gagaeetgeg tgtaceecac teageecagt gtggeecaga 120
agaactggta catcagcaag aaccccaagg acaagaggca tgtctggttc ggcgagagca 180
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tgaccgatgg attccagttc gagtatggcg gccagggctc cgaccctgcc gatgtggacc 240
tcggccgcga ccacgct
<210> 208
<211> 257
<212> DNA
<213> Homo sapiens
<400> 208
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ctggaatcca teggteatge tetegeegaa ecagacatge etettgteet tggggttett 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggtetcacc 180
agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tggggacetg 240
cccgggcggc cgctcga
<210> 209
<211> 747
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 453, 538, 540, 542, 546, 554, 556, 598, 659, 670, 679, 689,
693, 711, 723, 724, 731, 747
<223> n = A, T, C or G
<400> 209
tegageggee geeegggeag gtecaccaca cecaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacecae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgaggaacat ggntttagge ggaccacace gcccacaacg 480
gecacececa taaggeatag gecaagaeca taeeegeega atgtaggaea agaagetntn 540
tntcanacac catntnatgg geoccattee aggacactte tgagtacate atttatgnea 600
tetgtggcac ttgatgaaaa ceettacagt teagggttet ggaactttta ceaggeetnt 660
tacaggactn ggccggacnc cttaagccna ttncaccctg gggcgttcta nggtcccact 720
cgnncactgg ngaaaatggc tactgtn
<210> 210
<211> 872
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 165, 174, 181, 256, 260, 269, 271, 277, 286, 289, 294, 298,
300, 301, 303, 308, 311, 321, 325, 328, 329, 333, 338, 342,
346, 349, 351, 357, 359, 364, 366, 379, 385, 395, 396, 397,
407, 408, 410, 414, 415, 429, 431, 434, 435, 440, 443
<223> n = A, T, C or G
<221> misc_feature
<222> 444, 446, 447, 448, 449, 450, 451, 464, 470, 472, 475, 479,
483, 484, 485, 488, 494, 496, 497, 504, 508, 509, 511, 513,
517, 522, 524, 526, 532, 533, 542, 543, 553, 559, 566, 567,
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571, 572, 578, 582, 588, 591, 594, 595, 596, 600, 606
\langle 223 \rangle n = A,T,C or G
<221> misc feature
<222> 612, 614, 617, 618, 629, 630, 631, 652, 654, 655, 661, 663,
664, 666, 671, 673, 678, 679, 681, 688, 690, 691, 698, 706,
707, 708, 714, 719, 721, 723, 726, 741, 751, 761, 762, 769,
770, 778, 779, 781, 782, 785, 791, 802, 807, 808, 812
<223> n = A, T, C or G
<221> misc feature
<222> 815, 820, 827, 828, 838, 841, 844, 851, 857, 864, 866, 869,
\langle 223 \rangle n = A,T,C or G
<400> 210
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gegttacaaa etectaggag ggettgetgt geggagggee tgetatggtg tgetgeggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgngaaac tccnaggaca 180
ngagggctaa attccatgaa gtttgtggat ggcctgatga tccacaatcg gagaccctgt 240
taactactac cgtctnaccn cctgctqtnc ncccccnttt ctgctnaana catngggntn 300
ntnettgnee nteettgggt ngaanatnna atngeetnee enttentane netaetngnt 360
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aaccctatna nttnnattan atnntnnnnn netcacccc etenteattn ancenatang 480
ctnnnaantc cttnanncct ccenceennt nenctentac tnantnette tnneccatta 540
ennagetett tentttaana taatgnngee nngetetnea tntetaenat ntgnnnaatn 600
ccccnccc cnancgnntt tttgacctnn naacctcctt tcctcttccc tncnnaaatt 660
nennanttee nentteenne nttteggntn nteceatnet tteeannnet teantetane 720
nenetneaac ttatttteet nteatecett nttetttaea nneeceetnn tetaetenne 780
nnttncatta natttgaaac tnccacnnct anttncctcn ctctacnntt ttattttncg 840
ntenetetae ntaatanttt aatnanttnt en
<210> 211
<211> 517
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 462, 464, 506
<223> n = A, T, C or G
<400> 211
tegageggee geeegggeag gtetgeeaag gagaceetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tatctcatct ttgggttcca caatgctcac gtggtcaggc aggggcttct tagggccaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacaa gcagtgtcaa cgtagtaagt taacagggtc tccgctgtgg 300
atcatcagge catccacaaa cttcatggat ttagccctct gtcctcggag tttcccagac 360
accacaacct cgcagccttt ggccccactc tccatgatga accgcagcac accatagcag 420
geeeteegea caageaagee eteetaagaa tttgtaaege ananaetetg etggeaatgg 480
cacacaaacc tctagtggac ctcggncgcg accacgc
<210> 212
<211> 695
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 432, 476, 522, 547, 621, 624, 647, 679
<223> n = A,T,C or G
<400> 212
tegageggee geeegggeag gtetggteea ggatageetg egagteetee tactgetaet 60
ccagacttga catcatatga atcatactgg ggagaatagt tctgaggacc agtagggcat 120
gattcacaga ttccaggggg gccaggagaa ccaggggacc ctggttgtcc tggaatacca 180
gggtcaccat ttctcccagg aataccagga gggcctggat ctcccttggg gccttgaggt 240
ccttgaccat taggagggcg agtaggagca gttggaggct gtgggcaaac tgcacaacat 300
tetecaaatg gaatttetgg gttggggeag tetaattett gateegteae atattatgte 360
ategeagaga aeggateetg agteaeagae acatatttgg catggttetg getteeagae 420
atetetatee gneataggae tgaccaagat gggaacatee teetteaaca agettnetgt 480
tgtgccaaaa ataatagtgg gatgaagcag accgagaagt anccagctcc cctttttgca 540
caaagentea teatgtetaa atateagaca tgagaettet ttgggcaaaa aaggagaaaa 600
agaaaaagca gttcaaagta nccnccatca agttggttcc ttgcccnttc agcacccggq 660
ccccqttata aaacacctng ggccggaccc ccctt
<210> 213
<211> 804
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 552, 555, 592, 624, 629, 633, 658, 695, 697, 698, 700, 702,
745, 753, 755, 762, 773, 786, 788, 793, 795
<223> n = A,T,C or G
<400> 213
agcgtggtcg cggccgaggt gttttatgac gggcccggtg ctgaagggca gggaacaact 60
tgatggtgct actttgaact gcttttcttt tctccttttt gcacaaagag tctcatgtct 120
gatatttaga catgatgagc tttgtgcaaa aggggagctg gctacttctc gctctgcttc 180
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cagaaattcc atttggagaa tgttgtgcag tttgcccaca gcctccaact gctcctactc 420
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ctgggagaaa tggtgaccct ggtattccag gacaaccagg gtcccctggt tctcctggcc 540
cccctggaat cnggngaatc atgccctact ggtcctcaaa ctattctccc anatgattca 600
tatgatgtca agtctgggat agcnagtang ganggactcg caggctattc tggaccanac 660
ctgccggggg ggcgttcgaa agcccgaatc tgcananntn cnttcacact ggcggccgtc 720
gagctgcttt aaaagggcca ttccnccttt agngnggggg antacaatta ctnggcggcg 780
ttttanancg cgngnctggg aaat
<210> 214
<211> 594
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 452, 509, 585
<223> n = A,T,C or G
<400> 214
agcgtggtcg cggccgaggt.ccacatcggc agggtcggag ccctggccgc catactcgaa 60
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ctggaatcca teggtcatgc tetegeegaa ccagacatgc etettgteet tggggttett 120
getgatgtac cagttettet gggecacact gggetgagtg gggtacacge aggteteace 180
agtctccatg ttgcagaaga ctttgatggc atccaggttg cagccttggt tggggtcaat 240
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<210> 215
<211> 590
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9
<223> n = A, T, C or G
<400> 215
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congecte etggacete tggtecect ggteeteen gegetggttt egactteage 120
ttcctgcccc agccacctca agagaaggct cacgatggtg gccgctacta ccgggctgat 180
gatgecaatg tggttegtga eegtgacete gaggtggaca eeaceeteaa gageetgage 240
cagcagateg agaacateeg gageecagag ggeageegea agaaceeege eegeaeetge 300
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caaggetgea acctggatge catcaaagte ttetgeaaca tggagactgg tgagacetge 420
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gacaagaggc atgtctggtt cggcgagagc atgaccgatg gattccagtt cgagtatggc 540
ggccagggct cccaccctgc cgatgtggac ctccggccgc gaccaccctt
<210> 216
<211> 801
<212> DNA
<213> Homo sapiens
<221> misc feature
\langle 222 \rangle 2, 2\overline{2}, 25, 26, 328, 373, 385, 440, 473, 534, 571, 572, 573,
582, 587, 589, 593, 600, 605, 617, 633, 642, 653, 672, 681, 685, 696, 699, 709, 715, 717, 726, 731, 739, 742, 745, 758, 769, 772, 778, 780, 788, 789, 791, 793, 796
<223> n = A, T, C or G
<400> 216
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gtgaagatgg tcaccctgga aaacccggac gacctggtga gagaggagtt gttggaccac 120
aggqtgctcg tggtttccct ggaactcctg gacttcctgg cttcaaaggc attaggggac 180
acaatggtct ggatggattg aagggacagc ccggtgctcc tggtgtgaag ggtgaacctg 240
qtqcccctqq tqaaaatqqa actccaqqtc aaacaqqagc ccqtqqqctt cctqqtqaqa 300
gaggaccgtg ttggtqcccc tqqcccanac ctcggccgcg accacgctaa gcccgaattt 360
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ttaantgaaa teegeenaee eeeggggaaa agneggtttg engtattggg genettttte 660
cctttcctcg gnttacttga nttantgggc tttggncgnt tcgggttgng gcgancnggt 720
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aaaacatnng ncnaangggc t
<210> 217
<211> 349
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 10, 157, 170
<223> n = A, T, C or G
<400> 217
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gcccacgggc tcctgtttga cctggagttc cattttcacc aggggcacca ggttcaccct 120
tcacaccagg agcaccgggc tgtcccttca atccatncag accattgtgn cccctaatgc 180
ctttgaagcc aggaagtcca ggagttccag ggaaaccacc gagcaccctg tggtccaaca 240
actectetet caccaggteg teegggtttt ecagggtgae catetteace ageettgeea 300
ggaggaccag caggaccagc gttaccaacc tgcccgggcg gccgctcga
<210> 218
<211> 372
<212> DNA
<213> Homo sapiens
<400> 218
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gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa qcctgattca gacattcgtt cccactcatc 180
tecaacqqca taatqqqaaa etqtqtaqqq qteaaaqeac gagteateeg taggttggtt 240
caageetteg ttgacagagt tgeecaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 219
<211> 374
<212> DNA
<213> Homo sapiens
<400> 219
agcqtqqtcg cqgccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctqaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaagget tgaaccaacc tacggatgac tegtgetttg accectacac agttteccat 180
tatqccqttq qaqatqaqtq qqaacqaatq tctqaatcaq gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaag atgtgattca tctagatggt gccatgacaa 300
tggtgtgaac tacaagattg gagagaagtg ggaccgtcag ggagaaaatg gacctgcccg 360
ggccggccgc tcga
<210> 220
<211> 828
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 9, 557, 571, 587, 588, 601, 642, 643, 647, 654, 664, 681,
688, 698, 719, 720, 725, 734, 738, 743, 744, 757, 765, 773,
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778, 780, 782, 783, 793, 798, 805, 809, 822, 827
<223> n = A, T, C or G
<400> 220
tcqaqcqnnc qcccqgqcag qtccagtagt gccttcggga ctgggttcac ccccaggtct 60
geggeagttg teacagegee ageceegetg geetecaaag catgtgcagg ageaaatgge 120
accgagatat teettetgee actgttetee täegtggtat gtetteeeat categtaaca 180
cqttqcctca tqaqqqtcac acttqaattc tccttttccq ttcccaagac atgtqcagct 240
catttqqctq gctctatagt ttqqqqaaaq tttqttqaaa ctqtqccact gacctttact 300
tecteettet etactggage tttegtacet tecaettetg etgttggtaa aatggtggat 360
cttctatcaa tttcattgac agtacccact tctcccaaac atccagggaa atagtgáttt 420
cagagcgatt aggagaacca aattatgggg cagaaataag gggcttttcc acaggttttc 480
ctttggagga agatttcagt ggtgacttta aaagaatact caacagtgtc ttcatcccca 540
tagcaaaaga agaaacngta aatgatggaa ngcttctgga gatgccnnca tttaagggac 600
neceagaact teaceateta caggacetae tteagtttae annaagneae atantetgae 660
tcanaaagga cccaagtagc nccatggnca gcactttnag cctttcccct ggggaaaann 720
ttacnttett aaaneetngg eenngaeece ettaagneea aattntggaa aantteentn 780
cnnctggggg gengttenac atgentttna agggeceaat tneccent
<210> 221
<211> 476
<212> DNA
<213> Homo sapiens
<400> 221
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teteeggetg eccattgete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctqacc tqqttcttgg tcatctcctc ccqqqatggg gqcagggtgt 180
acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctq 240
qqaqqqcttt qttqqaqacc ttqcacttqt actccttqcc attcaqccaq tcctqqtqca 300
ggacggtgag gacgctgacc acacggtacg tgctgttgta ctgctcctcc cgcggctttg 360
tettggcatt atgeacetee acgeegteea egtaceagtt gaacttgace teagggtett 420
cgtggctcac gtccaccacc acgcatgtaa cctcagacct cggccgcgac cacgct
<210> 222
<211> 477
<212> DNA
<213> Homo sapiens
<400> 222
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ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
ccccatcqaq aaaaccatct ccaaagccaa agggcaagcc ccgagaacca caggtgtaca 300
ccctqcccc atcccgggag gagatgacca agaaccaggt cagcctgacc tgcctggtca 360
aaggetteta teecagegac ategeegtgg agtgggagag caatgggcag ceggagaaca 420
actacaagac cacgecteec gtgctggact ccgacacctg cccgggcggc cgctcga
<210> 223
<211> 361
<212> DNA
<213> Homo sapiens
<400> 223
tcgagcggcc gcccgggcag gttgaatggc tcctcgctga ccaccccggt gctggtggtg 60
ggtacagagc tccgatgggt gaaaccattg acatagagac tgtccctgtc cagggtgtag 120
gggcccagct cagtgatgcc gtgggtcagc tggctcagct tccagtacag ccgctctctg 180
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tccagtccag ggcttttggg gtcaggacga tgggtgcaga cagcatccac tctggtggct 240
geceeateet teteaggeet gageaaggte agtetgeaac cagagtacag agagetgaca 300
ctggtgttct tgaacaaggg cataagcaga ccctgaagga cacctcggcc gcgaccacgc 360
                                                                   361
<210> 224
<211> 361
<212> DNA
<213> Homo sapiens
<400> 224
agcqtqqtcg.cgqccqagqt qtccttcagq qtctqcttat qcccttqttc aaqaacacca 60`
gtgtcagctc tctgtactct gqttgcagac tqaccttgct caggcctgag aaggatgggg 120
cagccaccag agtggatgct gtctgcaccc atcgtcctga ccccaaaagc cctggactgg 180
acagagageg getgtactgg aagetgagee agetgaceca eggeateact gagetgggee 240
cctacaccct ggacagggac agtctctatg tcaatggttt cacccatcgg agctctgtac 300
ccaccaccag caccggggtg qtcaqcqaqg agccattcaa cctqccqqq cqqccqctcq 360
                                                                   361
<210> 225
<211> 766
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 574, 610, 631, 643, 657, 660, 666, 688, 712, 735, 747
<223> n = A, T, C or G
<400> 225
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actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagetgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
teagggeaat gacataaatt gtatattegg teeeggttee aggeeagtaa tagtageete 540
tgtgacacca gggcggggcc gagggaccet tctnttggaa gagaccaget tctcatactt 600
gatgatgagn ccggtaatcc tggcacgtgg nggttgcatg atnccaccaa ggaaatnggn 660
gggggnggac etgeceggeg geegttenaa ageceaatte cacacacttg gnggeegtac 720
tatggatece actengteca acttggngga atatggcata actttt
                                                                   766
<210> 226
<211> 364
<212> DNA
<213> Homo sapiens
<400> 226
tegageggee geeegggeag gteettgace tttteageaa gtgggaaggt gtaateegte 60
tccacagaca aggccaggac tcgtttgtac ccgttgatga tagaatgggg tactgatgca 120
acaqttgggt agccaatctg cagacagaca ctgqcaacat tgcggacacc ctccaggaag 180
cgaqaatgca gagtttcctc tgtgatatca agcacttcaq ggttgtagat gctgccattg 240
tegaacaeet getggatgae caqeecaaag gagaaggggg agatgttgag catgtteage 300
agegtggett egetggetee eactitigiet eeagtetiga teagaceteg geegegaeea 360
cgct
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<210> 227
<211> 275
<212> DNA
<213> Homo sapiens
<400> 227
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ggtgaccgtg ccctccagca acttcggcac ccagacctac acctgcaacg tagatcacaa 120
gcccagcaac accaaggtgg acaagagagt tgagcccaaa tettgtgaca aaactcacac 180
atgcccaccg tgcccagcac ctgaactcct ggggggaccg tcagtcttcc tcttcccccg 240
catececett ccaaacetge cegggeggee geteg
<210> 228
<211> 275
<212> DNA
<213> Homo sapiens
<400> 228
cgagcggccg cccgggcagg tttggaaggg ggatgcgggg gaagaggaag actgacggtc 60
ecceeaggag tteaggtget gggcaeggtg ggcatgtgtg agttttgtea caagatttgg 120
geteaactet ettgteeace ttggtgttge tgggettgtg atetaegttg caggtgtagg 180
tetgggtgee gaagttgetg gagggeaegg teaceaeget getgagggag tagagteetg 240
aggactgtag gacagacete ggeegegace aeget
<210> 229
<211> 40
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1, 4, 5, 13, 15, 17, 29
<223> n = A, T, C or G
<400> 229
nggnnggtcc ggncngncag gaccactcnt cttcgaaata
                                                                 40
<210> 230
<211> 208
<212> DNA
<213> Homo sapiens
<400> 230
agcgtggtcg cggccgaggt cctcacttgc ctcctgcaaa gcaccgatag ctgcgctctg 60
tttgcgaatc agaagttcag tggacttctg ataacgtcta atttcacgga gcgccacagt 180
accaggacct gcccgggcgg ccgctcga
<210> 231
<211> 208
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 33
\langle 223 \rangle n = A, T, C or G
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<400> 231
tegageggee geeegggeag gteetggtae tgnggegete egtgaaatta gaegttatea 60
quagticcact gaacttctga ttcgcaaact tcccttccag cgtctggtgc gagaaattgc 120
teaggaettt aaaacagate tgegetteea gagegeaget ateggtgett tgeaggagge 180-
aagtgaggac ctcggccgcg accacgct
<210> 232
<211> 332
<212> DNA
<213> Homo sapiens
<400> 232
togagogoc geooggoag gtocacatog geagggtogg ageoctggco geoatactog 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccaqteteca tqttqcaqaa qactttqatq qcatecaqqt tqcaqeettq qttqqqqtca 240
atccaptact ctccactctt ccaptcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gcggggttct tgacctcggc cgcgaccacg ct
                                                                   332
<210> 233
<211> 415
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 15, 19, 21
<223> n = A, T, C \text{ or } G
<400> 233
qtqqqnttga accentttna neteegettg qtaecgaget eqqateeact aqtaacqqee 60
gccaqtgtgc tggaattcgg cttagcgtgg tcgcggccga ggtcaagaac cccgcccqca 120
cctgccgtga cctcaagatg tgccactctg actggaagag tggagagtac tggattgacc 180
ccaaccaagg ctgcaacctg gatgccatca aagtcttctg caacatggag actggtgaga 240
cctgcgtgta ccccactcag cccagtgtgg cccagaagaa ctggtacatc agcaagaacc 300
ccaaggacaa gaggcatgtc tggttcggcg agagcatgac cgatggattc cagttcgagt 360
atggcggcca gggctccgac cctgccgatg tggacctgcc cgggcggccg ctcga
<210> 234
<211> 776
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 505, 550, 574, 601, 604, 608, 612, 649, 656, 657, 680, 711,
750, 776
<223> n = A, T, C or G
<400> 234
agcqtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacaqcta ccatcaqcqq ccttaaacct qqaqttqatt ataccatcac tqtqtatqct 180
qtcactqqcc qtqqaqacag ccccqcaagc agcaagccaa tttccattaa ttaccqaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aaqtqqctqc cttcaaqttc ccctqttact qqttacagag taaccaccac tcccaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt aagtgtctat gctcagaatc caagcggaga 480
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gaagtcagcc tetggttcag actgnaagta accaacattg atcgcctaaa ggactggcat 540
tcactgatgn ggatgccgat tccatcaaaa ttgnttggga aaacccacag gggcaagttt 600
ncangtonag gnggacctac togagecetg aggatggaat cottgactnt toottnnoot 660
qatqqqqaaa aaaaaccttn aaaacttgaa ggacctgccc gggcggccgt ncaaaaccca 720
attccaccc cttgggggcg ttctatgggn cccactcgga ccaaacttgg ggtaan
<210> 235
<211> 805
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 637, 684, 705, 724, 733, 756, 778, 793, 796, 804
\langle 223 \rangle n = A,T,C or G
<400> 235
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agggaatage teatggatte catecteagg getegagtag gteaccetgt acctggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg gcatccacat cagtgaatgc 180
cagtccttta gggcgatcaa tgttggttac tgcagtctga accagaggct gactctctcc 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
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gggagtggtg gttactctgt aaccagtaac aggggaactt gaaggcagcc acttgacact 420
aatgctgttg tcctgaacat cggtcacttg catctgggat ggtttgtcaa tttctgttcg 480
gtaattaatg gaaattggct tgctgcttgc ggggcttgtc tccacggcca gtgacagcat 540
acacagtgat ggtataatca actccaggtt taagccgctg atggtagctg aaactttgct 600
ccaggcacaa gtgaactcct gacagggcta tttcctnctg ttctccgtaa gtgatcctgt 660
aatateteae tqqqacaqea gganqeatte caaaaetteg ggegngacee cetaageega 720
attntgcaat atncatcaca ctggcgggcg ctcgancatt cattaaaagg cccaatcncc 780
                                                                   805
cctataggga gtntantaca attng
<210> 236
<211> 262
<212> DNA
<213> Homo sapiens
tcqaqcqqcc qcccqqqcaq gtcacttttg gtttttggtc atgttcggtt ggtcaaagat 60
aaaaactaag tttgagagat gaatgcaaag gaaaaaaata ttttccaaag tccatgtgaa 120
attgtctccc attittttgg cttttgaggg ggttcagttt gggttgcttg tctgtttccg 180
ggttggggg aaagttggtt gggtgggagg gagccaggtt gggatggagg gagtttacag 240
gaagcagaca gggccaacgt cg
<210> 237
<211> 372
<212> DNA
<213> Homo sapiens
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aacqaagget tgaaccaacc taeggatgac tegtgetttg acceetacac agttteccat 180
tatgccqttq gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
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<210> 238
<211> 372
<212> DNA
<213> Homo.sapiens
<400> 238
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aaaqcctaaq cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caagcetteg ttgacagagt tgeecaeggt aacaacetet teecgaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 239
<211> 720
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 478, 557, 563, 566, 620, 660, 663, 672, 673, 684, 693, 695
<223> n = A, T, C or G
<400> 239
tegagegee geeeggeag qtecaceata agteetgata caaccaegga tgagetgtca 60
ggagcaaggt tgatttettt cattggteeg gtetteteet tggggggteac eegeactega 120
tatecagiga getgaacatt gggtggtgte caetgggege teaggettgt gggtgtgaee 180
tgagtgaact tcaggtcagt tggtgcagga atagtggtta ctgcagtctg aaccagaggc 240
tgactetete egettggatt etgageatag acaetaacea eataeteeae tgtgggetge 300
aagcetteaa tagteattte tgtttgatet ggacetgeag ttttagtttt tgttggteet 360
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cacttgacac taatgctgtt gtcctgaaca teggtcactt gcatctggga tggtttgnca 480
atttctgttc ggtaattaat ggaaattggc ttgctgcttg cggggctgtc tccacggcca 540
qtqacaqcat acacaqqat qqnatnatca actccaagtt taaggccctg atggtaactt 600
taaacttgct cccaqccagn qaacttccgg acagggtatt tcttctggtt ttccgaaagn 660
gancetggaa tnnteteett ggancagaag gancnteeaa aacttgggee ggaaceeett 720
<210> 240
<211> 691
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 564, 582, 640, 651, 666, 669, 690
<223> n = A, T, C or G
<400> 240
agegtggteg eggeegaggt cetgteagag tggcactggt agaagtteea ggaaccetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatgqtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatqttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaaqctqaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
qttqqqqaaq ctcqtctqtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
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tcagggcaat gacataaatt gtatattcgg ttcccggttc caggccagta atagtagcct 540
cttgtgacac caggcggggc ccanggacca cttctctggg angagaccca gcttctcata 600
cttgatgatg taacccggta atcctgcacg tggcggctgn catgatacca ncaaggaatt 660
gggtgnggng gacctgcccg gcggccctcn a
<210> 241
<211> 808
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 680, 715, 721, 728, 735, 749, 757, 762, 772, 776, 779, 781,
792, 796, 800, 808
<223> n = A, T, C or G
<400> 241
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acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
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gaaattgaca aaccateeca gatgeaagtg accgatgtte aggacaacag cattagtgte 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt agtgtctatg ctcagaatcc aagcggagag 480
agtcagecte tggttcagae tgcagtaace actatteetg caccaactga cetgaagtte 540
acteaggtea cacceacaag cetgageege cagtggacae cacceaatgt teacteactg 600
gatatcgagt gcgggtgacc cccaaggaga agacccggac ccatgaaaga aatcaacctt 660
getectgaca geteateegn gggtgtatea ggacttatgg gggactgeec eggenggeeg 720
ntegaaaneg aattnigaaa itteettene aetgggngge gnitegaget inetiniana 780
nggcccaatt cncctntagn gggtcgtn
                                                                   808
<210> 242
<211> 26
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22
<223> n = A, T, C or G
<400> 242
agcgtggtcg cggccgaggt cnagga
                                                                   26
<210> 243
<211> 697
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 496, 541, 624, 662, 679, 688
<223> n = A, T, C or G
<400> 243
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ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
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gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacecettt egteacecae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgaggaacat ggttttagge ggaccacace geccacaacg 480
ggcaccccca taaggnatag gccaagacca taccccgccg aatgtaggac aagaagctct 540
nteteaacaa ceateteatg ggeeceatte caggacaett etgagtaeat cattteatgt 600
catcetggtg ggcacttgat gaanaaccet tacagttcag ggtteetgga acttetacca 660
gngccacttc tgacagganc ttgggcgnga ccaccct
<210> 244
<211> 373
<212> DNA
<213> Homo sapiens
<400> 244
agegtggteg eggeegaggt ccattttete cetgaeggte ceaettetet ccaatettgt 60
agttcacacc attgtcatgg caccatctag atgaatcaca tctgaaatga ccacttccaa 120
agectaagea etggeacaac agtttaaage etgatteaga eattegttee eacteatete 180
caacggcata atgggaaact gtgtaggggt caaagcacga gtcatccgta ggttggttca 240
ageettegtt gacagagttg cecaeggtaa caacetette eegaacetta tgeetetget 300
ggtctttcag tgcctccact atgatgttgt aggtggcacc tctggtgagg acctgcccgg 360
gcggcccgct cga
<210> 245
<211> 307
<212> DNA
<213> Homo sapiens
<400> 245
agcgtggtcg cggccgaggt gtgccccaga ccaggaattc ggcttcgacg ttggccctgt 60
ctgcttcctg taaactccct ccatcccaac ctggctccct cccacccaac caactttccc 120
cccaacccgg aaacagacaa gcaacccaaa ctgaaccccc tcaaaagcca aaaaaatggg 180
agacaatttc acatggactt tggaaaatat ttttttcctt tgcattcatc tctcaaactt 240
agtttttatc tttgaccaac cgaacatgac caaaaaccaa aagtgacctg cccgggcggc 300
cqctcqa
<210> 246
<211> 372
<212> DNA
<213> Homo sapiens
<400> 246
tegageggee geeegggeag gteetcacea gaggtgeeae etacaacate atagtggagg 60
cactgaaaga ccagcagagg cataaggttc gggaagaggt tgttaccgtg ggcaactctg 120
tcaacgaagg cttgaaccaa cctacggatg actcgtgctt tgacccctac acagtttccc 180
attatgccgt tggagatgag tgggaacgaa tgtctgaatc aggctttaaa ctgttgtgcc 240
agtgcttagg ctttggaagt ggtcatttca gatgtgattc atctagatgg tgccatgaca 300-
atggtgtgaa ctacaagatt ggagagaagt gggaccgtca gggagaaaat ggacctcggc 360
cgcgaccacg ct
                                                                   372
<210> 247
<211>.348
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc feature
<222> 284, 297, 299, 322, 325, 338, 342, 345
\langle 223 \rangle n = A, T, C or G
<400> 247
tegageggee geeegggeag gtaceggggt gqteagegag gagecattea caetqaactt 60
caccatcaac aacctgcggt atgaggagaa catgcagcac cctggctcca ggaagttcaa 120
caccacggag agggtccttc agggcctgct caggtccctg ttcaagagca ccaqtgttgg 180
ccctctgtac tctggctgca gactgacttt gctcagacct gagaaacatg gggcagccac 240
tggagtggac gccatctgca ccctccgcct tgatcccact ggtnctggac tggacanana 300
geggetatac ttgggagetg ancenaacet ttggeggnga encenett
<210> 248
<211> 304
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 125
<223> n = A, T, C or G
<400> 248
gaggactggc tcagctccca gtatagccgc tctctgtcca gtccaggacc agtgggatca 60
aggeggaggg tgeagatgge gtecacteea gtggetgeee eatgtttete aagtetgage 120
aaagncagtc tgcagccaga gtacagaggg ccaacactgg tgctcttgaa cagggacctg 180
agcaggccct gaaggaccct ctccgtggtg ttgaacttcc tggagccagg gtgctgcatg 240
ttctcctcat accgcaggtt gttgatggtg aagttcagtg tgaatggctc ctcgctgacc 300
accc
<210> 249
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 308, 310, 312, 320, 331, 336, 383, 392, 396
<223> n = A, T, C or G
<400> 249
agcgtggtcg cggccgaggt ccaccacac caattccttg ctggtatcat ggcagccgcc 60
acgtgccagg attaccggct acatcatca gtatgagaag cctgggtctc ctcccagaga 120
agtggtccct cggccccgcc ctggtgtcac agaggctact attactggcc tggaaccggg 180
aaccgaatat acaatttatg tcattgccct gaagaataat cagaagagcg agcccctgat 240
tggaaggaaa aagacagacg agcttcccca actggtaacc cttccacacc ccaatcttca 300
tggaccanan ancttggatn gtcctttcac nggttnaaaa aacccttttc gccccccac 360
cttqqqqatt aaccttqqqa aanqqqqatt tnaccnttcc
                                                                  400
<210> 250
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 338, 357, 361, 369, 388, 394
<223> n = A, T, C or G
```

```
<400> 250
tcgagcggcc gcccgggcag gtcctgtcag agtggcactg gtagaagttc caggaaccct 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
egggtatggt ettggeetat geettatggg ggtggeegtt gtgggeggtg tggteegeet 240
aaaaccatgt teeteaaaga teattigtig eecaacactg ggtigetgae eagaagtgee 300
aggaagetga ataccattte cagtgteata eccagggngg gtgaccaaag ggggtenttt 360
ngacctggng aaaggaacca tccaaaanct ctgncccatg
<210> 251
<211> 514
<212> .DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 107, 312, 338, 351, 352, 357, 363, 366, 373, 380, 405,
421, 444, 508
<223> n = A, T, C or G
<400> 251
agegtggneg eggeegaggt etgaggatgt aaactettee eaggggaagg etgaagtget 60
gaccatggtg ctactgggtc cttctgagtc agatatgtga ctgatgngaa ctgaagtagg 120
tactgtagat ggtgaagtet.gggtgteeet aaatgetgea tetecagage ettecateat 180
taccgtttct tcttttgcta tgggatgaga cactgttgag tattctctaa agtcaccact 240
gaaatettee teeaaaggaa aacetgtgga aaageeeett atttetgeee cataatttgg 300
ttctcctaat cnctctgaaa tcactatttc cctggaangt ttgggaaaaa nngggcnacc 360
tgncantgga aantggatan aaagatccca ccattttacc caacnagcag aaagtgggaa 420
nggtaccgaa aagctccaag taanaaaaag gagggaagta aaggtcaagt gggcaccagt 480
ttcaaacaaa actttcccca aactatanaa ccca
<210> 252
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 20, \overline{2}1, 25, 44, 343, 347, 356, 362, 387, 391, 398, 409, 428,
430, 453, 494
<223> n = A, T, C \text{ or } G
<400> 252
aagcggccgc ccgggcaggn ncagnagtgc cttcgggact gggntcaccc ccaggtctgc 60
ggcagttgtc acagcgccag ccccgctggc ctccaaagca tgtgcaggag caaatggcac 120
cgagatattc cttctgccac tgttctccta cgtggtatgt cttcccatca tcgtaacacg 180
ttgcctcatg agggtcacac ttgaattctc cttttccgtt cccaagacat gtgcagctca 240
tttggctggc tctatagttt ggggaaagtt tgttgaaact gtgccactga cctttacttc 300
ctccttctct actggagctt tccgtacctt ccacttctgc tgntggnaaa aagggnggaa 360
cntcttatca atttcattgg acagtanccc nctttctncc caaaacatnc aagggaaaat 420
attgattncn agagcggatt aaggaacaac ccnaattatg ggggccagaa ataaaggggg 480
cttttccaca ggtnttttcc t
                                                                    501
<210> 253
<211> 226
<212> DNA
<213> Homo sapiens
```

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<400> 253
tegageggee geeegggeag gtetgeagge tattgtaagt gttetgagea catatgagat 60
aacctgggcc aagctatgat gttcgatacg ttaggtgtat taaatgcact tttgactgcc 120
atctcagtgg atgacagcct tctcactgac agcagagatc ttcctcactg tgccagtggg 180
caggagaaag agcatgctgc gactggacct cggccgcgac cacgct
<210> 254
<211> 226
<212> DNA
<213> Homo sapiens
<400> 254
agggtggtcg cggccgaggt ccaqtcgcag catgctcttt ctcctgccca ctggcacagt 60
qaqqaaqatc tctqctqtca qtqaqaaqqc tqtcatccac tqaqatqqca qtcaaaaqtq 120
catttaatac acctaacqta tcqaacatca taqcttqqcc caggttatct catatqtqct 180
cagaacactt acaatagcct gcagacctgc ccgggcggcc gctcga
<210> 255
<211> 427
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 327, 403
<223> n = A, T, C or G
<400> 255
egageggeeg ceegggeagg teeagactee aatecagaga accaceaage cagatgteag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aagatctacc tgtacacctt 120
gaatgacaat geteggaget eeeetgtggt categaegee tecaetgeea ttgatgeaee 180
atccaacctg cgtttcctgg ccaccacacc caattccttg ctggtatcat ggcagccgcc 240
acqtqccaqq attaccqqct acatcatcaa qtatqaqaaq cctqqqtctc ctcccaqaqa 300
agtggtccct cggccccgcc ctggtgncac agaagctact attactggcc tggaaccggg 360
aaccgaatat acaatttatg tcattgccct gaagaataat canaagagcg agcccctgat 420
tggaagg
                                                                   427
<210> 256
<211> 535
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 456, 475
\langle 223 \rangle n = A, T, C or G
<400> 256
agegtggteg eggeegaggt cetgteagag tggcaetggt agaagtteea ggaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct gtctttttcc 180
ttccaatcaq qqqctcqctc ttctqattat tcttcaqqqc aatgacataa attqtatatt 240
cqqttcccqq ttccaqqcca gtaataqtag cctctqtgac accaggqcgg ggccqaggga 300
ccacttetet qqqagqaqac ccaggettet catacttgat gatgtaneeg gtaateetgg 360
caccytggcg gctgccatga taccagcaag gaattgggtg tggtggccaa gaaacgcagg 420
ttggatggtg catcaatggc agtggaggcg tcgatnacca caggggagct ccgancattg 480
tcattcaagg tggacaggta gaatcttgta atcaggtgcc tggtttgtaa acctg
```

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<210> 257
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 495, 511
<223> n = A, T, C or G
<400> 257
tegageggee geeegggeag gtttegtgae egtgaeeteg aggtggaeae cacceteaag 60
agcctgagcc agcagatega gaacatecgg agcccagagg gcagecgcaa gaacceegcc 120
cqcacctqcc qtqacctcaa qatqtqccac tctqactgga aqagtqgaga qtactggatt 180
gaccccaacc aaggetgeaa cetggatgee ateaaagtet tetgeaacat ggagaetggt 240
gagacetgcg tgtaccccac tcagcccagt gtggcccaga agaactggta catcagcaag 300
aaccccaagg acaagaagca tgtctggttc ggcgaaagca tgaccgatgg attccagttc 360
gagtatggcg gccagggctc cgaccctgcc gatgtggacc tcggccgcga ccacgctaag 420
cccgaattcc agcacactgg cggccgttac tagtgggatc cgagcttcgg taccaagctt 480
ggcgtaatca tgggncatag ctgtttcctg ngtgaaaatg gtattccgct tcacaatttc 540
ccac
<210> 258
<211> 418
<212> DNA
<213> Homo sapiens
<400> 258
agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
qctqatqtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tggggtcaat 240
ccaqtactct ccactcttcc aqtcagagtg gcacatcttg aggtcacggc aggtgcgggc 300
qqqqttcttq cgqctgccct ctggqctccg gatgttctcg atctgctggc tcaagctctt 360
gaagggtggt gtccacctcg aggtcacggt cacgaaacct gcccgggcgg ccgctcga
<210> 259
<211> 377
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 320, 326, 342, 352
<223> n = A, T, C or G
<400> 259
agcgtggtcg cggccgaggt caagaacccc gcccgcacct gccgtgacct caagatgtgc 60
cactctgact ggaagagtgg agagtactgg attgacccca accaaggctg caacctggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
gccgatgtgg acctgcccgn gccggnccgc tcgaaaagcc cnaatttcca gncacacttg 360
geeggeegtt actactg
                                                                   377
<210> 260
<211> 332
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<212> DNA
<213> Homo sapiens
<400> 260
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgacetegge egegaceaeg et
<210> 261
<211> 94
<212> DNA
<213> Homo sapiens
<400> 261
tttttttt tttttttt ttttttt
<210> 262
<211> 650
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 412, 582, 612, 641, 646
\langle 223 \rangle n = A,T,C or G
<400> 262
agogtggtog oggoogaggt otggoattoo ttoqacttot otocagooga gottoccaga 60
acatcacata tcactgcaaa aatagcattg catacatgga tcaggccagt ggaaatgtaa 120
agaaggccct gaagctgatg gggtcaaatg aaggtgaatt caaggctgaa ggaaatagca 180
aattcaccta cacagttctg gaggatggtt gcacgaaaca cactggggaa tggagcaaaa 240
cagtetttga atategaaca egeaaggetg tgagactace tattgtagat attgcaceet 300
atgacattgg tggtcctgat caagaatttg gtgtggacgt tggccctgtt tgctttttat 360
aaaccaaact ctatctgaaa tcccaacaaa aaaaatttaa ctccatatgt gntcctcttg 420
ttctaatctt ggcaaccagt gcaagtgacc gacaaaattc cagttattta tttccaaaat 480
gtttggaaac agtataattt gacaaagaaa aaaggatact tetettttt tggctggtcc 540
accaaataca attcaaaagg ctttttggtt ttattttttt anccaattcc aatttcaaaa 600
tgtctcaatg gngcttataa taaaataaac tttcaccctt nttttntgat
<210> 263
<211> 573
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 453, 458, 544
<223> n = A, T, C or G
<400> 263
agggtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct qtccaqqaqt tcactqtqcc tqqqaqcaaq 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
```

```
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagaa qtaaccacca ctcccaaaaa 360
tggaccagga ccaacaaaaa ctaaaactgc aggtccagat caaacagaaa atggactatt 420
gaaggettge ageccaeagt ggaagtatgt ggntaggngt etatgeteag aateccaage 480
eggagaaagt cageettetg gtttagaetg cagtaaceaa cattgatege cetaaaggae 540
tggncattca cttggatggt ggatgtccaa ttc
<210> 264
<211> 550
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 39, 174, 352, 526
<223> n = A, T, C or G
<400> 264
tegageggee geeegggeag gteettgeag etetgeagng tettetteae cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagngaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga accagagget gaetetetee 240
gettggatte tgageataga cactaaceae atactecaet gtgggetgea ageetteaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tggtggtcct gncccatttt 360
tgggaagtgg ggggttactc tgtaaccagt aacaggggaa cttgaaggca gccacttgac 420
actaatgctg ttgtcctgaa catcggtcac ttgcatctgg ggatggtttt gacaatttct 480
ggttcggcaa attaatggaa attggcttgc tgcttggcgg ggctgnctcc acgggccaqt 540
gacagcatac
<210> 265
<211> 596
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 352, 353, 534, 555, 587
<223> n = A, T, C or G
<400> 265
tegageggee geeegggeag gteettgeag etetgeagtg tettetteac cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcq acatccacat cagtqaatqc 180
cagtccttta gggcgatcaa tgttggttac tgcagtctga accagaggct gactctctcc 240
gettggatte tgageataga cactaaceae atacteeaet gtgggetgea ageetteaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tgttggncct gnnccatttt 360
tggggaaggg gtggttactc ttgtaaccag taacagggga acttgaagca qccacttgac 420
actaatgctg gtggcctgaa catcggtcac ttgcatctgg gatggtttgg tcaatttctg 480
tteggtaatt aatgggaaat tggettaetg gettgegggg getgteteea eggneagtga 540
caagcataca caggngatgg gtataatcaa ctccaggttt aaggccnctg atggta
<210> 266
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
```

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<222> 393, 473
<223> n = A, T, C \text{ or } G
<400> 266
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agtaagccaa tttccattaa ttaccgaaca 240
qaaattqaca aaccatccca qatqcaaqtq accqatqttc aqqacaacaq cattaqtqtc 300
aaqtqqctqc cttcaaqttc ccctqttact qqttacaqaq taaccaccac tcccaaaaat 360
qqqaccaqqa ccaacaaaaa actaaaactg canqqtccaq atcaaacaqa aatqactatt 420
gaaggettge ageceaeagt ggagtatgtg ggttagtgte tatgeteaga atnecaageg 480
gagagagtca gcctctggtt cagact
<210> 267
<211> 548
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 346, 358, 432, 510, 512
<223> n = A, T, C \text{ or } G
<400> 267
tegageggee geeegggeag gteagegete teaggaegte accaceatgg cetgggetet 60
getectecte accetectea eteagggeae agggteetgg geceagtetg ecetgaetea 120
geeteectee gegteegggt eteetggaca gteagteace ateteetgea etggaaceag 180
cagtgacqtt ggtgcttatg aatttgtctc ctggtaccaa caacacccag gcaaggcccc 240
caaactcatg atttctgagg tcactaagcg gccctcaggg gtccctgatc gcttctctgg 300
ctccaagtct ggcaacacgg cctccctgac cgtctctggg ctccangctg aggatgangc 360
tgattattac tggaagetea tatgeaggea acaacaattg ggtgttegge ggaagggaee 420
aagetgaceg thetaaggte aageceaagg ettgeeece teggteacte tgtteceace 480
ctcctctgaa gaagctttca agccaacaan gncacactgg gtgtgtctca taagtggact 540
ttctaccc
<210> 268
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 98, \overline{3}80, 421, 454, 495, 506, 512, 561, 565, 579
<223> n = A, T, C or G
<400> 268
agegtggteq eggeegaggt etgtagette tgtgggaett ceaetgetea ggeqteagge 60
teaggtaget getggeegeg tacttgttgt tgetttgntt ggagggtgtg gtggteteea 120
ctcccgcctt gacggggctg ctatctgcct tccaggccac tgtcacggct cccgggtaga 180
agtcacttat gagacacacc agtgtggcct tgttggcttg aagctcctca gaggagggtg 240
ggaacagagt gaccgagggg gcagccttgg gctgacctag gacggtcagc ttggtccctc 300
egeegaacae ecaattgttg ttgeetgeat atgagetgea gtaataatea geeteateet 360
cagcctggag cccagagacn gtcaagggag gcccgtgttt gccaagactt ggaaqccaga 420
naagcgatca gggacccctg agggccgctt tacngacctc aaaaaatcat gaatttgggg 480
qqcctttqcc tqqqnqttqq ttqqtnacca qnaaaacaaa atttcataaa gcaccaacqt 540
cactgctggt ttccagtgca ngaanatggt gaactgaant gtcc
                                                                    584
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<210> 269
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 265, 329
\langle 223 \rangle n = A, T, C or G
<400> 269
agegtggteg eggeegaggt ceageateag gageeeegee ttgeeggete tggteatege 60
ctttcttttt gtggcctgaa acgatgtcat caattcgcag tagcagaact gccgtctcca 120
ctgctgtctt ataagtctgc agettcacag ccaatggctc ccatatgccc agttccttca 180
tgtccaccaa agtacccgtc tcaccattta caccccaggt ctcacagttc tcctgggtgt 240
gcttggcccg aagggaggta agtanacgga tggtgctggt cccacagttc tggatcaggg 300
tacgaggaat gacetetagg geetgggena caageeetgt atggacetge eegggeggge 360
ccgctcga
<210> 270
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 54, 163, 219, 229, 316
<223> n = A, T, C or G
tegageggee geeegggeag gtecataeag ggetgttgee eaggeeetag aggneattee 60
ttgtaccetg atccagaact gtgggaccag caccatecgt ctacttacet ccetteggge 120
caagcacacc caggagaact gtgagacctg gggtgtaaat ggngagacgg gtactttggt 180
ggacatgaag gaactgggca tatgggagcc attggctgng aagctgcana cttataagac 240
agcagtggag acggcagttc tgctactgcg aattgatgac atcgtttcag gccacaaaaa 300
gaaaggegat gaccanagee ggcaaggegg ggetteetga tgetggaeet eggeegeega 360
ccacqctt
<210> 271
<211> 424
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 279, 329, 362, 384, 400
<223> n = A, T, C or G
<400> 271
agcgtggtcg cggccgaggt ccactagagg tctgtgtgcc attgcccagg cagagtctct 60
qcqttacaaa ctcctaggag ggcttqctgt qcqqaqqqcc tqctatqqtg tqctqcqqtt 120
catcatggaq aqtggggcca aaqqctgcga qqttgtqqtq tctggqaaac tccgaggaca 180
gagggetaaa tecatgaagt ttgtggatgg cetgatgate cacageggag accetgttaa 240
ctactacgtt gacactgctg tgcgccacgt gttgctcana cagggtgtgc tgggcatcaa 300
ggtgaagatc atgctgccct gggacccanc tggcaaaaat ggcccttaaa aaccccttgc 360
entgaceacg tgaaccattt gtgngaacce caagatgaan atacttgeec accacecee 420
attc
```

```
<210> 272
<211> 541
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 422, 442, 510, 513, 515, 525
\langle 223 \rangle n = A,T,C or G
<400> 272
tegageggee geeegggeag gtetgeeaag gagaeeetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtqgcag 120
tateteatet ttgggtteea eaatgeteae gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag cagtgtcaac gtagtagtta acagggtctc cgctgtggat 300
catcaggcca tecacaaact teatggattt agecetetgt ceteggagtt teceaaaaca 360
ccacaacctc gccagccttt gggccccact tcttcatgaa tgaaaccgca gcacaccatt 420
ancaaggeee tteegeacag gnaageeett eetaaggagt titgtaaaeg caaaaaaete 480
ttgcctgggg caaatgggca cacagacctn tantnggacc ttggnccgcg aaccaccgct 540
<210> 273
<211> 579
<212> DNA ·
<213> Homo sapiens
<220>
<221> misc feature
<222> 223, 265, 277, 308, 329, 346, 360, 366, 429, 448, 517, 524,
<223> n = A, T, C or G
<400> 273
agegtggteg eggeegaggt etggeeetee tggeaagget ggtgaagatg gteaecetgg 60
aaaacccgga cgacctggtg agagaggagt tgttggacca cagggtgctc gtggtttccc 120
tggaactcct ggacttcctg gcttcaaagg cattagggga cacaatggtc tggatggatt 180
gaagggacag cccggtgctc ctggtgtgaa gggtgaacct ggngcccctg gtgaaaatgg 240
aactccaggt caaacaggag cccgnggget teetggngag agaggacgtg ttggtgeecc 300
tggcccanac ctgcccgggc ggccgctcna aaagccgaaa tccagnacac tggcggccgn 360
tactantgga atccgaactt cggtaccaaa gcttggccgt aatcatggcc atagcttgtt 420
ccctggggng gaaattggta ttccgctncc aattccacac aacataccga acccggaaag 480
cattaaagtg taaaagccct gggggggcct aaatgangtg agcntaactc ncatttaatt 540
ggcgttgcgc ttcactgccc cgcttttcca qtccgggna
                                                                   579
<210> 274
<211> 330
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 171
<223> n = A, T, C or G
<400> 274
tegageggee geeegggeag gtetgggeea ggggeaceaa eaegteetet eteaeeagga 60
agcccacggg ctcctgtttg acctggagtt ccattttcac caggggcacc aggttcaccc 120
```

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ttcacaccag gagcaccggg ctgtcccttc aatccatcca gaccattgtg ncccctaatg 180
cctttgaagc caggaagtcc aggagttcca gggaaaccac gagcaccctg tggtccaaca 240
actectetet caccaggteg teegggtttt ceagggtgae catetteace ageettgeca 300
ggagggccag acctcggccg cgaccacgct
<210> 275
<211> 97
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 2, 35, 72
<223> n = A, T, C or G
<400> 275
ancgtggtcg cggccgaggt cctcaccaga ggtgncacct acaacatcat agtggaggca 60
ctgaaagacc ancagaggca taaggttcgg gaagagg
<210> 276
<211> 610
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 358, 360, 363, 382, 424, 433, 464, 468, 477, 491, 499, 511,
558, 584, 588, 590
<223> n = A, T, C or G
<400> 276
tegageggee gecegggeag gtecatttte teeetgaegg teceaettet etceaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgtecaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcngn 360
congaacaac gottaagccc gnattotgca gaataatccc atcacacttg geggccgctt 420
cgancatgca tcntaaaagg ggccccaatt tcccccttat aagngaancc gtatttncca 480
atttcactgg necegecgnt tttacaaacg neggtgaact ggggaaaaac eetggeggtt 540
acccaacttt aatcgccntt ggcagcacaa tccccccttt tcgnccancn tgggcgtaaa 600
taaccgaaaa
                                                                   610
<210> 277
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 5, 18, 21, 31
<223> n = A, T, C or G
<400> 277
ancgnggtcg cggccgangt nttttttttttt
                                                                  38
<210> 278
<211> 443
```

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<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 156, 212, 233, 245, 327, 331, 336, 361, 364, 381, 391, 397,
419, 437
<223> n = A, T, C or G
<400> 278
agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaaqacaaa 120
geogegggag gageagtaca acageacgta ceggggggte agegteetea cegteetgea 180
ccagaattgg ttgaatggca aggagtacaa qngcaaggtt tccaacaaag ccntcccagc 240
ccccntcgaa aaaaccattt ccaaagccaa agggcagccc cqaqaaccac aggtgtacac 300
cctgcccca tcccgggagg aaaagancaa naaccnggtt cagccttaac ttgcttqqtc 360
naangetttt tateeeaaeg naetteeeee ntggaantgg gaaaaaeeaa tgggeeaane 420
cgaaaaacaa ttacaanaac ccc
<210> 279
<211> 348
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 219, 256, 291, 297, 307, 314, 317
<223> n = A, T, C or G
tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60
tetecggetg eccattgete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtga 180
acacctgggg ttctcggggc ttgccctttg gttttgaana tggttttctc gatggggct 240
ggaagggett tgttgnaaac cttgcacttg actccttgcc attcacccag nectggngca 300
ggacggngag gacnetnace acacggaace gggetggtgg actgetce
                                                                   348
<210> 280
<211> 149
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 18, 34, 51, 118, 120, 140
<223> n = A, T, C or G
<400> 280
agegtggteg eggacgangt cetgteagag tggnaetggt agaagtteea ngaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcaqaagngn 120
cctggaatgg ggcccatgan atggttgcc
                                                                   149
<210> 281
<211> 404
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 383, 386, 388, 393
<223> n = A, T, C or G
<400> 281
tegageggee geeegggeag gtecaceaea cecaatteet tgetggtate atggeageeg 60
ccacqtqcca ggattaccqq ctacatcatc aaqtatqaqa aqcctqqqtc tcctcccaqa 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactqg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt eggeacceec 360
cctgggtatg aacctgggaa aanggnantt aanctttcct ggca
<210> 282
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 320, 341, 424, 450, 459, 487, 498
<223> n = A, T, C or G
<400> 282
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
qaaattqaca aaccatccca qatqcaaqtq accqatqttc aqqacaacaq cattaqtqtc 300
aaqtgqctqc cttcaaggtn ccctqqtact qqqttacaqa ntaaccacca ctcccaaaaa 360
tggaccagga accacaaaaa cttaaactgc agggtccaga tcaaaacaga aatgactatt 420
gaangettge ageecacagt gggagtatgn gggtagtgne tatgetteag aateeaageg 480
gaaaaangtc aagccttntg ggttcaa
<210> 283
<211> 325
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 216, 292, 303, 304
<223> n = A, T, C or G
<400> 283
togagoggeo geoogggeag gteettgeag etetgeagtg tettetteae cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttae tgeagnetga accagagget gaetetetee 240
gettggatte tgageataga cactaaceae atacteeaet gtgggetgea ancetteaat 300
aanncatttc tgtttgatct ggacc
                                                                   325
<210> 284
<211> 331
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
\langle 222 \rangle 54, \overline{5}9, 63, 121, 312, 327
<223> n = A, T, C or G
<400> 284
tegageqqee qeeegggeaq qtetqgtggq qteetqqeac acqeacatgq gqqnqttqnt 60
ctnatecage tgeecagece ceattggega gtttgagaag gtgtgeagea atgaeaacaa 120
nacettegae tetteetgee aettetttge cacaaagtge aecetggagg geaceaagaa 180
gggccacaag ctccacctgg actacatogg gccttgcaaa tacatccccc cttgcctgga 240
ctctgagctg accgaattcc cccttgcgca tgcgggactg gctcaagaac cgtcctggca 300
cccttgtatg anagggatga agacacnacc c
<210> 285
<211> 509
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 316, 319, 327, 329, 339, 344, 357, 384, 398, 427, 443, 450,
<223> n = A, T, C or G
<400> 285
agcqtqqtcq cqqccqaqqt ctqtcctaca qtcctcaqqa ctctactccc tcaqcaqcqt 60
ggtgaccgtg ccctccagca acttcggcac ccagacctac acctgcaacg tagatcacaa 120
gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180
atgcccaccg tgcccagcac etgaactcet ggggggaccg tcagtettee tetteccccg 240
catececett ccaaacetge ccgggcggcc getegaaage cgaattecag cacaetggcg 300
gccggtacta gtgganccna acttggnanc caacctggng gaantaatgg gcataanctg 360
tttctggggg gaaattggta tccngtttac aattcccnca caacatacga gccggaagca 420
taaaagngta aaagcctggg ggnggcctan tgaagtgaag ctaaactcac attaattngc 480
gttgccgctc actggcccgc ttttccagc
<210> 286
<211> 336
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 188, 251, 267
<223> n = A, T, C or G
<400> 286
tegageggee geeegggeag gtttggaagg gggatgeggg ggaagaggaa gaetgaeggt 60
cccccagga gttcaggtgc tgggcacggt gggcatgtgt gagttttgtc acaagatttg 120
ggctcaactc tcttgtccac cttggtgttg ctgggcttgt gatctacgtt gcaggtgtag 180
gtctgggngc cgaagttgct ggagggcacg gtcaccacgc tgctgaggga gtagagtcct 240
gaggactgta ngacagacct cggccgngac cacgctaagc cgaattctgc agatatccat 300
cacactggcg gccgctccga gcatgcattt tagagg
                                                                    336
<210> 287
<211> 30
<212> DNA
<213> Homo sapiens
<220>
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```
<221> misc feature
<222> 8, 18
\langle 223 \rangle n = A, T, C or G
<400> 287
                                                                     30
agcgtggncg cggacganga caacaacccc
<210> 288
<211> 316
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 130
\langle 223 \rangle n = A,T,C or G
<400> 288
tegageggee geeegggeag gneeaeateg geagggtegg agecetggee geeatacteg 60
aactggaatc catcggtcat gctcttgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgn accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact etccactett ecagtcagag tggcacatet tgaggtcacg gcaggtgcgg 300
gcggggttct tgacct
<210> 289
<211> 308
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 36, 165, 191, 195, 218, 235
\langle 223 \rangle n = A,T,C or G
<400> 289
agegtggteg eggeegaggt ecageetgga gataanggtg aaggtggtge eceeggaett 60
ccaggtatag ctggacctcg tggtagccct ggtgagagag gtgaaactgg ccctccagga 120
cctgctggtt tccctggtgc tcctggacag aatggtgaac ctggnggtaa aggagaaaga 180
ggggctccgg ntganaaagg tgaaggaggc cctcctgnat tggcaggggc cccangactt 240
agaggtggag ctggcccccc tggccccgaa ggaggaaagg gtgctgctgg tcctcctggg 300
ccacctgg
<210> 290
<211> 324
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 184
<223> n = A, T, C or G
<400> 290
tegageggee geeegggeag gtetgggeea ggaggaceaa taggaeeagt aggaeeett 60
gggccatett tecetgggac accateagea cetggacege etggtteace ettgteacee 120
tttggaccag gacttccaag acctcctctt tctccaggca ttccttgcag accaggagta 180
ecancageae caggtggeee aggaggaeea geageaeeet tteeteette gggaeeaggg 240
```

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ggaccagete cacetetaag teetggggee cetgecaate caggagggee teetteacet 300
ttctcacccg gagcccctct ttct
<210> 291
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 249, 267
<223> n = A, T, C or G
<400> 291
tegageggee geeegggeag gtecaeeggg atattegggg gtetggeagg aatgggagge 60
atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cgacaaccgg aggctggaga gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt cagagactgg agccattact tcaagatcat cgaggacctg 240
agggeteana tettegeaaa taetgengae aatgeeeg
<210> 292
<211> 299
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 19, 25, 51, 53, 61, 63, 70, 109, 136, 157, 241, 276
<223> n = A, T, C or G
<400> 292
atgegnggte geggeegang accanetetg geteataett gaetetaaag nenteaceag 60
nanttacggn cattgccaat ctgcagaacg atgcgggcat tgtccgcant atttgcgaag 120
atctgagccc tcaggncctc gatgatcttg aagtaanggc tccagtctct gacctggggt 180
ccettettet ecaagtgete ceggattttg etetecagee teeggttete ggtetecaag 240
netteteact etgteeagga aaagaggeea ggeggnegat eagggetttt geatggaet 299
<210> 293
<211> 101
<212> DNA
<213> Homo sapiens
<400> 293
ttttttttt tttttttt tttttttt ttttttt t
                                                               101
<210> 294
<211> 285
<212> DNA
<213> Homo sapiens
<220> .
<221> misc_feature
<222> 64, 103, 110, 237, 282
<223> n = A, T, C or G
tegageggee geeegggeag gtetgeeaac accaagattg geeeeegeeg catecacaca 60
```

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gttngtgtgc ggggaggtaa caagaaatac cgtgccctga ggntggacgn ggggaatttc 120
tcctggggct cagagtgttg tactcgtaaa acaaggatca tcgatgttgt ctacaatgca 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatngac 240
agcacaccgt accgacagtg ggtaccgaag teceactatg enect
<210> 295
<211> 216
<212> DNA
<213> Homo sapiens
<400> 295
tegageggee geeegggeag gtecaceaea eccaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaag·
<210> 296
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 10, 33, 61, 62, 63, 88, 109, 122, 255, 298, 307, 340,
355, 386, 393
<223> n = A,T,C or G
agggtqntcn cggccgagga tggggaaget cgnctgtett tttccttcca atcagggget 60
nnntcttctg attattcttc agggcaanga cataaattgt atattcggnt cccggttcca 120
gnccagtaat agtagcctct gtgacaccag ggcggggccg agggaccact tctctgggag 180
gagacccagg cttctcatac ttgatgatga agccggtaat cctggcacgt gggcggctgc 240
catgatacca ccaangaatt gggtgtggtg gacctgcccg ggcgggccgc tcgaaaancc 300
gaattentge aagaatatee ateacacttg ggegggeegn tegaaccatg catentaaaa 360
gggccccaat ttccccccta ttaggngaag ccncatttaa caaattccac ttgg
<210> 297
<211> 376
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 312, 326, 335, 361
<223> n = A, T, C or G
<400> 297
tegageggee geeegggeag gtetegeggt egeactggtg atgetggtee tgttggteec 60
eccqgeete etggaetee tgqteeceet qqteeteea qeqetqqttt eqaetteaqe 120
ttcctgcccc agccacctca agaqaaggct cacgatggtq gccgctacta ccgqqctqat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagccttgag 240
ccagcagaat cgaaaacatt cggaacccaa gaagggcaag cccgcaaaga aaccccgccc 300
gcacctggcc gngaacctcc aagaangtgc ccacntettg actgggaaaa aaagggaaaa 360
ntacttggaa ttggac
<210> 298
<211> 357
<212> DNA
```

```
<213> Homo sapiens
<220>
<221> misc_feature
<222> 345, 346
<223> n = A, T, C or G
<400> 298
agegtggteg eggeegaggt ceaeategge agggteggag eeetggeege catactegaa 60
ctggaatcca teggteatge tetegeegaa ccagacatge etettgteet tgggqttett 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggtetcacc 180
agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tggggtcaat 240
ccagtactet ccactettee agteagaagt ggeacatett gaggteaegg cagggtgegg 300
geggggttet tgegggetge cettetggge teeeggaatg ttetnngaae ttgetgg
<210> 299
<211> 307
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 281, 285, 306
<223> n = A, T, C or G
<400> 299
agegtggteg eggeegaggt ceactagagg tetgtgtgee attgeecagg eagagtetet 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tqctatqqtq tqctqcqqtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 240
ctactacgtt gacacttgct tgtgcgccac gtgttgctca nacangggtg ggctgggcat 300
caaggng
                                                                   307
<210> 300
<211> 351
<212> DNA
<213> Homo sapiens
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tateteatet ttgggtteca caatgeteac gtggteagge aggggettet tagggecaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag caagtgtcaa cgtaagtaag ttaacagggt ctccgctgtg 300
gatcatcagg ccatccacaa acttcatgga tttaaccctc tgtcctcgga q
<210> 301
<211> 330
<212> DNA
<213> Homo sapiens
<400> 301
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agtgctggtg gtgggcacag aggtccgatg ggtgaaacca ttgacataga gactgttcct 120
gtccagggtg taggggccca gctctttgat gccattggcc agttggctca gctcccagta 180
cagecgetet etgttgagte eagggetttt ggggteaaga tgatggatge agatggcate 240
cactccagtg gctgctccat ccttctcgga cctgagagag gtcagtctgc agccagagta 300
cagagggcca acactggtgt tctttgaata
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<210> 302-
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 129, 295
<223> n = A, T, C or G
<400> 302
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agetgggeec ctacaccetg gacaggaaca qtetetatgt caatggttte acceateaga 120
gctctgtgnc caccaccagc actcctggga cctccacagt ggatttcaga acctcaggga 180
ctccatcctc cctctccagc cccacaatta tggctgctgg ccctctcctg gtaccattca 240
ccctcaactt caccatcacc aacctgcagt atggggagga catgggtcac cctgnctcca 300
ggaagttcaa caccaca
<210> 303
<211> 283
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 139, 146, 195
<223> n = A, T, C or G
<400> 303
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ggtctggcac cctgagcagt ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggnt ctgagnctgt gggatagctg ccatgaagta acctgaagga 180
ggtgctggct ggtangggtt gattacaggg ttgggaacag ctcgtacact tgccattctc 240
tgcatatact ggttagtgag gtgagcctgg ccctcttctt ttg
<210> 304
<211> 72
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 59
<223> n = A, T, C or G
<400> 304
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ctgctggtcc tg
<210> 305
<211> 245
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 5, 11, 22, 98, 102
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95

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<223> n = A, T, C or G
<400> 305
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ctcctctttc tcctttagca ccaggttgac cagcagenec ancaggacca gcaaatccat 120
tggggccagc aggaccgacc tcaccacgtt caccagggct tccccgagga ccagcaggac 180
cagcaggacc agcagcccca gcttcgcccc ggtcacctgt ggctcacctc ggccgcgacc 240
acqct
<210> 306
<211> 246
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 144, 159
<223> n = A, T, C or G
<400> 306
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atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cganaaccgg aggctggana gcaaaatccg ggagcacttg 180
qaqaaqaaqq gaccccaggt caaqaqactg gagccattac ttcaagatca tcgagggacc 240
tggagg
<210> 307
<211> 333
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 5
\langle 223 \rangle n = A,T,C or G
<400> 307
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ctgagcctc aggtectega tgatettgaa gtaatggete cagtetetga eetggggtee 180
cttcttctcc aagtgctccc ggattttgct ctccagcctc cggttctcgg tctccaggct 240
ceteactetg tecaggtaag aaggeecagg eggtegttea ggetttgeat ggteteette 300
tegttetgga tgeeteecat teetgeeaga eee
<210> 308
<211> 310
<212> DNA
<213> Homo sapiens
<400> 308
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gatcagtcag actggctgtt ctcagttctc acctgagcaa ggtcagtctg cagccagagt 180
acagagggcc aacactggtg ttcttgaaca agggcttgag cagaccctgc agaaccctct 240
tccqtqqtgt tgaacttcct ggaaaccagg gtgttgcatg tttttcctca taatgcaagg 300
ttggtgatgg
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<210> 309

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<211> 429
<212> DNA
<213> Homo sapiens
<400> 309
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gctgatgtac cagttettet gggccacact gggctgagtg gggtacaccg caggteteac 180
cagtetecat gttgcagaag actttgatgg catecaggtt gcageettgg ttggggtcaa 240
tocagtacte tecactette cagteagaag tgggcacate ttgaggtcae eggcaggtge 300
eggeegggg gttettgegg ettgeeetet gggeteegga tgttetegat etgettgget 360
caggetettg agggtgggtg tecacetega ggteaeggte aeegaaacet geeegggegg 420
cccgctcga
<210> 310
<211> 430
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 342
<223> n = A,T,C or G
<400> 310
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gaccccaacc aaggctgcaa cctggatgcc atcaaagtct tctgcaacat ggagactggt 240
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<210> 311
<211> 2996
<212> DNA
<213> Homo sapiens
<400> 311
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cctacaccct ggacagggac agtctctatg tcaatggttt cacacagcgg agctctgtgc 180
ccaccactag cattectggg acccccacag tggacctggg aacatetggg actccagttt 240
ctaaacctgg teectegget gecageeete teetggtget atteactete aactteacea 300
teaceaacet geggtatgag gagaacatge ageaecetgg etecaggaag tteaacacea 360
eggagagggt cetteaggge etggteeetg tteaagagea eeagtgttgg eeetetgtae 420
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tgggagctga gccagetgac ccacaatatc actgagctgg gcccctatgc cctggacaac 600
gacageetet tigteaatgg titeaeteat eggagetetg tgteeaeeae eageaeteet 660
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cqccctqacc ccacaggccc tgggctggac agagagcagc tgtatttgga gctgagccag 1020
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ggctccctca agttcaacat cacagacaac gtcatgaagc acctgctcag tcctttgttc 1260
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ggagaataca acgtccagca acagtgccca ggctactacc agtcacacct agacctggag 2880
gatetgeaat gaetggaact tgeeggtgee tggggtgeet tteeceeage cagggteeaa 2940
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<210> 312
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<212> PRT
<213> Homo sapiens
<400> 312
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Leu Gly Pro Pro Gln Trp Thr Trp Glu His Leu Gly Leu Gln Phe Leu
Asn Leu Val Pro Arg Leu Pro Ala Leu Ser Trp Cys Tyr Ser Leu Ser
                            40
Thr Ser Pro Ser Pro Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu
                        55
Ala Pro Gly Ser Ser Thr Pro Arg Arg Gly Ser Phe Arg Ala Trp Ser
                    70
                                        75
Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu
                85
                                    90
Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala
                                105
Ile Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu
                            120
                                                125
Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu
                        135
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Gly Pro Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn Gly Phe Thr

145					150					155					160
His	Arg	Ser	Ser	Val 165	Ser	Thr	Thr	Ser	Thr 170	Pro	Gly	Thr	Pro	Thr 175	Val
Tyr	Leu	Gly	Ala 180	Ser	ГЛS	Thr	Pro	Ala 185	Ser	Ile	Phe	Gly	Pro 190	Ser	Ala
Ala	Ser	His 195	Leu	Leu	Ile	Leu	Phe 200	Thr	Leu	Asn	Phe	Thr 205	Ile	Thr	Asn
	210	_				215	Trp		_		220	_			
225					230		Leu			235					240
				245			Gly	_	250					255	
		·	260				Gly	265					270		
		275					Leu 280	_	_			285	-		
	290					295	Ile				300		_		
305					310		Asn	_		315		_			320
				325			.Val		330					335	
			340			_	Asp	345		•		_	350		
		355					360 Leu				-	365			
	370					375	Lys				380				
385					390		Pro			395					400
				405			Ser		410					415	
_			420				Lys	425				_	430		
		435					440 Pro					445			
Thr	450 Phe	Leu	Pro	Pro	Leu	455 Ser	Glu	Ala	Thr	Thr	460 Ala	Met	Gly	Tyr	His
465 Leu	Lys	Thr	Leu	Thr	470 Leu	Asn	Phe	Thr	Ile	475 Ser	Asn	Leu	Gln	Tyr	480 Ser
Pro	Asp	Met		485 Lys	Gly	Ser	Ala		490 Phe	Asn	Ser	Thr		495 Gly	Val
Leu	Gln		500 Leu	Leu	Arg	Pro	Leu	505 Phe	Gln	Ьуs	Ser		510 Met	Gly	Pro
Phe		515 Leu	Gly	Суѕ	Gln		520 Ile	Ser	Leu	Arg		525 Glu	Lys	Asp	Gly
Ala 545	530 Ala	Thr	Gly	Val	_	535 Thr	Thr	Cys	Thr	_	540 His	Pro	Asp	Pro	
	Pro	Gly	Leu	Asp 565	550 Ile	Gln	Gln	Leu	Tyr 570	555 Trp	Glu	Leu	Ser		560 Leu
Thr	His	Gly	Val 580		Gln	Leu	Gly	Phe 585	-	Val	Leu	Asp	Arg 590	575 Asp	Ser
Leu	Phe	Ile 595		Gly	Tyr	Ala	Pro 600		Asn	Leu	Ser	Ile 605		Gly	Glu
Tyr	Gln		Asn	Phe	His	Ile	Val	Asn	Trp	Asn	Leu		Asn	Pro	qeA

610 615 620 Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys 630 635 Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe 645 650 655 Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys 660 665 Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe 680 685 Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr 695 700 Gln, Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln 710 715 Pro Thr Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile 725 730 Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe 760 Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr 775 780 Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys 790 795 Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu 810 Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr 825 Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn 835 840 845 Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu 855 860 Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly 875 Val Leu Val Thr Thr Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val 890 Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp 905 Leu Gln

<210> 313

<211> 656

<212> DNA

<213> Homo sapiens

<400> 313

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<210> 314
<211> 519
<212> DNA
<213> Homo sapiens
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gtttaaggat ggtctcggtg gttaggccca ctagaataaa ctgagtccaa tacctctaca 180
cagttatgtt taactgggct ctctgacacc gggaggaagg tggcggggtt taqqtqttqc 240
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cattcattag ctaatggtgt cctttggtat ttattaaaat caccacagca tagggggact 360
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<210> 315
<211> 441
<212> DNA
<213> Homo sapiens
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cagaggcaac cagggtttat agtgctaggt aaatgtcatc tcttttgtgc tactgactca 180
ttgtcaaacg tetetgeact gttttcagcc tetecacgtt geetetgtee tgettettag 240
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atgatttaaa aattccaatg actttcgccc ttgggagaaa tttccaagga aatctctctc 360
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tacgaaaaaa tgcattttgt g
<210> 316
<211> 247
<212> DNA
<213> Homo sapiens
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ccagtctage ttggtaagaa gagagacatg cccccaacct cggcgccctt tttcctcacg 180
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<212> DNA
<213> Homo sapiens
<400> 317
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gaatgeteee tggaggeeet gtggegagga caggeactgg atggteeaga ceetetqqet 180
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ttgcattcta acactgggtc attaatgaca cctttccagt ggatgttgca aaaaccaaca 300
etgteaggaa cetggeeetg ggagggetea ggtgagetea caaggagagg teaageeaag 360
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<210> 318
<211> 320
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 1\overline{7}, 24, 271
<223> n = A, T, C or G
<400> 318
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gtcattggtc aggaagctgt cctggacgta ggccatctcc acatccatgg ggatgccata 180
gtcactgggc ctttgctcgg gaggaggcat cacccagaaa ggcgagatct tggactcggg 240
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gctggagccc tgcagccgca
<210> 319
<211> 212
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 172
<223> n = A, T, C or G
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accetgetge agacetegge egegaceaeg et
<210> 320
<211> 769
<212> DNA
<213> Homo sapiens
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tggagggcgt ctttctccat cagcgcatac tgagcagggg tactcagatc cttcttggaa 180
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cattcatagg cccaattacc ccctctctgg tcctacatgc attcttcttc ttcctgacca 360
cccctctgtt ctgaaccctc tcttcccgga qcctcccatt atattqcagq atgctcactt 420
acttgqtatg ttccagagat gccacatcat tcaggttgaa gacaatgatg atggcttgga 480
agagtggcag aaacagcccc aggttgacag ggaagacact actgctcatt tccccaatcc 540
ttccagetcc atatgagaaa gccatgtgca ctctgagacc cacetacccc acttcaccca 600
gccccttacc ttgagctcct ctatagtagg ttgatgcaat gcatttgaac ctctcctgcc 660
cagcggtatc ccaactggaa ggaaggaaga gtgaagcaca ggtatgtatc ttggggggtg 720
tgggtgctgg ggagaaggga tagctggaag gggtgtggaa gcactcaca
<210> 321
<211> 690
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> 633, 666
<223> n = A, T, C or G
<400> 321
tgggctgtgg gcggcacctg tgctctgcag gccagacagc gatagaagcc tttgtctgtg 60
cctactcccc cggaggcaac tgggaggtca acgggaagac aatcatcccc tataagaagg 120
gtgcctggtg ttcgctctgc acagccagtg tctcaggctg cttcaaagcc tgggaccatg 180
caggggget ctgtgaggtc cccaggaatc cttgtcgcat gagctgccag aaccatggac 240
qtctcaacat caqcacctgc cactgccact qtccccctgg ctacacgggc agatactgcc 300
aagtgaggtg cagcctgcag tqtqtgcacg gccggttccg ggaggaggag tgctcgtgcg 360
tctgtgacat cggctacggg ggagcccagt gtgccaccaa ggtgcatttt cccttccaca 420
cctgtgacct gaggatcgac ggagactgct tcatggtgtc ttcagaggca gacacctatt 480
acagaagcca ggatgaaatg tcagaggaat ggcggggtgc tggcccagat caagagccag 540
aaagtgcagg acatcctcgc cttctatctg ggccgcctgg agaccaccaa cgaggtgact 600
gacagtgact ttgagaccag gaacttctgg atngggctca cctacaagac cgccaaggac 660
teettneget gggccacagg ggagcaccag
<210> 322
<211> 104
<212> DNA
<213> Homo sapiens
<400> 322
gtcgcaagcc ggagcaccac catgtagcct ttcccgaagt accggacctt ctcctcctcc 60
                                                                   104
acgeteacat caeggacate atggageagg accaecacet ggte
<210> 323
<211> 118
<212> DNA
<213> Homo sapiens
<400> 323
gggccctggg cgcttccaaa tgacccagga ggtggtctgc gacgaatgcc ctaatgtcaa 60
actagtgaat gaagaacgaa cactggaagt agaaatagag cctggggtga gagacgga 118
<210> 324
<211> 354
<212> DNA
<213> Homo sapiens
<400> 324
tgctctccgg gagcttgaag aagaaactgg ctacaaaggg gacattgccg aatgttctcc 60
ageggtetgt. atggacccag gettgteaaa etgtactata cacategtga eagteaccat 120
taacggagat gatgccgaaa acgcaaggcc gaagccaaag ccaggggatg gagagtttgt 180
ggaagtcatt tctttaccca agaatgacct gctgcagaga cttgatgctc tggtagctga 240
agaacatete acagtggaeg ecagggteta tteetaeget etagegetga aacatgeaaa 300
tgcaaagcca tttgaagtgc ccttcttgaa attttaagcc caaatatgac actg
<210> 325
<211> 642
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<222> 1
\langle 223 \rangle n = A, T, C or G
<400> 325
ncatgettga atgggeteet ggtgagagat tgccccetgg tggtgaaaca atcqtqtgtg 60
cccactgata ccaagaccaa tgaaagagac acagttaagc agcaatccat ctcatttcca 120
ggcacttcaa taggtcgctg attggtcctt gcaccagcag tggtagtcgt acctatttca 180
gagaggtctg aaattcaggt tcttagtttg ccagggacag gccctacctt atattttttt 240
ccatcttcat catccacttc tgcttacagt ttgctgctta caataactta atgatggatt 300
gagttatctg ggtggtctct agccatctgg gcagtgtggt tctgtctaac caaagggcat 360
tggcctcaaa ccctgcattt ggtttagggg ctaacagagc tcctcagata atcttcacac 420
acatgtaact gctggagatc ttattctatt atgaataaga aacgagaagt ttttccaaag 480
tgttagtcag gatctgaagg ctgtcattca gataacccag cttttccttt tggcttttag 540
cccattcaga ctttgccaga gtcaagccaa ggattgcttt tttgctacag ttttctgcca 600
aatggcctag ttcctgagta cctggaaacc agagagaaag ag
<210> 326
<211> 455
<212> DNA
<213> Homo sapiens
<400> 326
tccgtgagga tgagcttcga gtccttcacc aggcactgca ggggcacagt cacgtcaatc 60
accttcacct tetegetett cetgetettg teattgacaa actteeegta eeaggeattg 120
acgatgatga ggcccattct ggactcttct gcctcaatta tccttcggac agattcctgc 180
atcagccgga cagcggactc cgcctcttgc ttcttctgca gcacatcggt ggcggcgctt 240
tecetetget tetecaatte ettetette tgageeetga ggtatggttt gatgateaga 300
cggtgcatgg caaagtagac cactagaggc cccacggtgg catagaacat ggcgctgggc 360
agaagetggt ccgtcaagtg aatagggaag aagtatgtct gactggccct gttgagettg 420
actttgagag aaacgccctg tggaactcca acgct
                                                                   455
<210> 327
<211> 321
<212> DNA
<213> Homo sapiens
<400> 327
ttcactgtga actcgcagtc ctcgatgaac tcgcacagat gtgacagccc tgtctccttq 60
ctctctgagt tctcttcaat gatgctgatg atgcagtcca cgatagcgcg cttatactca 120
aagccaccct cttcccgcag catggtgaac aggaagttca taaggacggc gtgtttgcga 180
ggatatttct gacacagggc actgatggcc tggacaacca ccaccttgaa ttcatccqag 240
atttctgaca tgaaggagga gatctgcttc atgaggcggt cgatgctgct ctcgctgccc 300
gtcttaagga gggtggtgat g
                                                                   321
<210> 328
<211> 476
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 302, 311
<223> n = A, T, C \text{ or } G
<400> 328
tgcaggaggg gccatggggg ctgtgaatgg gatgcagccc catggtgtcc ctgataaatc 60
cagtgtgcag tctgatgaag tctgggtggg tgtggtctac gggctggcag ctaccatgat 120
ccaagaggta atgcactcct tttcccatct ctccaccatc tgtatcctgg ccmagaaaaa 180
```

104

cttcccttca aaccaaccaa aatttccttt caaaggcata acccaaatgc catccttggt 240 coggetaat aaagceteec ceattittee cotggtatge atteceagge teectggeet 300 throughout netgeteting agreement tateteetee caettactag gageteetta 360 aaggcaaaga ctctactgcc tccatctatc cagtggaagt ggctcttcag agggtgccaa 420 gttagtatgt atgactgtca tctctcccaa cagggcctga cttggsaggg cttcca <210> 329 <211> 340 <212> DNA <213> Homo sapiens <400> 329 cgagggagat tgccagcacc ctgatggaga gtgagatgat ggagatcttg tcagtgctag 60 ctaagggtga ccacagecet gtcacaaggg ctgctgcage ctgcctggac aaagcagtgg 120 aatatgggct tatccaaccc aaccaagatg gagagtgagg gggttgtccc tgggcccaag 180 gctcatgcac acgctaccta ttgtggcacg gagagtaagg acggaagcag ctttggctgg 240 tggtggctgg catgcccaat actcttgccc atcctcgctt gctgccctag gatgtcctct 300 gttctgagtc agcggccacg ttcagtcaca cagccctgct <210> 330 <211> 277 <212> DNA <213> Homo sapiens <400> 330 tqtcaccatc acattqqtqc caaataccca qaaqacatcq taqatqaaqa qtccqcccaq 60 caggatgcag ccagtgctga cattgttgag gtgcaggagc tctactccat taagggagaa 120 ggccaggcca aaaaggttgt tggcaatcca qtqcttcctc aqcagqtacc aqacqccaac 180 gatgctgctc aggcccaggc acaccaggtc cttggtgtca aattcataat tgatgatctc 240 ctccttgttt tcccagaacc ctgtgtgaag agcagac 277 <210> 331 <211> 136 <212> DNA <213> Homo sapiens <400> 331 ttgettecea ceteetttet etgteetete etgaggttet geettacaat ggggacaetg 60 atacaaacca cacacacaat gaggatgaaa acagataaca ggtaaaatga cctcacctgc 120 ccgggcggcc gctcga 136 <210> 332 <211> 184 <212> DNA <213> Homo sapiens <400> 332 ttgtgagata aacgcagata ctgcaatgca ttaaaacgct tgaaatactc atcagggatg 60 ttgctgatct tattgttgtc taagtagaga gttagaagag agacagggag accagaaggc 120 agtetggeta tetgattgaa geteaagtea aggtattega gtgatttaag acetttaaaa 180 gcag 184 <210> 333 <211> 384 <212> DNA <213> Homo sapiens <400> 333

```
cggaaaactt cgaggaattq ctcaaagtgc tggqggtgaa tqtqatqctq aqqaaqattq 60
ctgtggctgc agcgtccaag ccagcagtgg agatcaaaca qqaqqqagac actttctaca 120
tcaaaacctc caccaccgtg cgcaccacag agattaactt caaqqttggg gaggagtttg 180
aggagcagac tgtggatggg aggccctgta agagcctggt qaaatgggag aqtgaqaata 240
aaatggtctg tgagcagaag ctcctgaagg gagagggccc caagacctcg tggaccagag 300
aactgaccaa cgatggggaa ctgatcctga ccatgacggc ggatgacgtt gtgtgcacca 360
gggtctacgt ccgagagtga gcgg
<210> 334
<211> 169
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 165
<223> n = A, T, C or G
<400> 334
cnacaaacag agcagacacc ctggatccgg tcctgctact ggccaggacg gctggaccgt 60
aaaattgaat ttccacttcc tgaccgccgc cagaagagat tgattttctc cactatcact 120
agcaagatga acctetetga ggaggttgac ttggaagaet atgtngeee
<210> 335
<211> 185
<212> DNA
<213> Homo sapiens
<400> 335
ccaggtttgc agcccaggct gcacatcagg ggactgcctc gcaatacttc atgctgttgc 60
tgctgactga tggtgctgtg acggatgtgg aagccacacg tgaggctgtg gtgcgtgcct 120
cgaacctgcc catgtcagtg atcattgtgg gtgtgggtgg tgctgacttt gaggccatgg 180
agcag
                                                                   185
<210> 336
<211> 358
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 26
<223> n = A, T, C or G
<400> 336
ctgcccctgc cttacggcgg ccaganacac acccaggatg gcattggccc caaacttgga 60
tttgttctca gtcccatcca actccagcat caggttgtcc agtttctctt gctccaccac 120
agagagacct gagctgatga gggctggcgo gatggtggag ttgatgtggt ccactgcctt 180
caggacacct ttgcctaagt aacgctgttt gtctccatcc ctcagctcca gggcctcata 240
gatgcccgta gaggctccac tgggcactgc agcccggaaa agacctttgg cagtatagag 300
atccacctcc actgtggggt tcccgcggga gtccaggatc tcccgggccc agatette
<210> 337
<211> 271
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 17
<223> n = A, T, C or G
<400> 337
cacaaagcca ccagccnggg aaatcagaat ttacttgatg caactgactt gtaatagcca 60
gaaatcctgc ccagcatggg attcagaacc tggtctgcaa ccaaatccac cgtcaaaqtt 120
catacaggat aaaacaaatt caattgcctt ttccacatta atagcatcaa gcttccccaa 180
caaagccaaa gttgccaccg cacaaaaaga gaatcttgtg tcaatttctc cctactttat 240
aaaagtagat ttttcacatc ccatgaagca g
<210> 338
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 17, 18
<223> n = A, T, C or G
<400> 338
etgtgeteec gaetngnnea teteaggtae caceqaetge actgggeggg geeetetggg 60
gggaaaggct ccacggggca gggatacatc tcgaggccag tcatcctctg gaggcagccc 120
aatcaggtca aagattttgc ccaactggtc ggcttcagag tttccacaga agagaggctt 180
tegacgaaac atetetgeaa agatacagee aacaeteeac atgtecacag gtgttgeata 240
tgtggactgc agaagaactt cgggagctcg gtaccagagt gtaacaacca cgggtgtaag 300
tgccatctgg tagctgtaga ttctgg
                                                                   326
<210> 339
<211> 260
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 47, 54, 60, 69, 90, 91, 96, 113, 117, 119, 195
<223> n = A, T, C or G
<400> 339
ttcacctgag gactcatttc gtgccctttg ttgacttcaa gcaaagncct tcanggtctn 60
caaggacgnc acatttccac ttgcgaatgn nctcanggct catcttgaag aanaagnanc 120
ccaagtgctg gatcccagac tcgggggtaa ccttgtgggt aagagctcat ccagtttatg 180
ctttaggacg tccanctact cgggggagct ggaagcctgc gtggatgcgg ccctgctgga 240
cctcggccgc gaccacgcta
<210> 340
<211> 220
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 18
<223> n = A, T, C or G
<400> 340
ctggaagece ggctnggnet ggcageggaa ggagecagge aggtteaege ageggtgetg 60
```

```
gcagtagcgg tagcggcact cgtctatgtc cacacactcg ggcccgatct tgcggtaacc 120
atcagggcag gtgcactgat aggagccagg caagttatgg cagtcctggc tggggcgaca 180
gtcgtgcagg gcctgggcac actcgtccac atccacacag
<210> 341
<211> 384
<212> DNA
<213> Homo sapiens
<400> 341
ctqctaccaq qqqaqcqaqa gctqactatc ccaqcctcgg ctaatgtatt ctacgccatg 60
gatggagett cacacgattt ceteetgegg cageggegaa ggteetetae tgetacaceg 120
qqcqtcacca gtggcccgtc tgcctcagga actcctccga gtgagggagg agggggctcc 180
tttcccagga tcaaggccac agggaggaag attgcacggg cactgttctg aggaggaagc 240
cccgttggct tacagaagtc atggtgttca taccagatgt gggtagccat cctgaatggt 300
ggcaattata tcacattgag acagaaattc agaaagggag ccagccaccc tggggcagtg 360
aagtgccact ggtttaccag acag
<210> 342
<211> 245
<212> DNA
<213> Homo sapiens
<400> 342
ctggctaagc tcatcattgt tactggtggg caccatgtcc ttgaagcttc aggcaagcaa 60
tgtaaccaac aagaatgacc ccaagtccat caactctcga gtcttcattg gaaacctcaa 120
cacagetetg gtgaagaaat cagatgtgga gaccatette tetaagtatg geegtgtgge 180
cggctgttct gtgcacaagg gctatgcctt tgttcagtac tccaatgagc gccatgcccg 240
ggcag
<210> 343
<211> 611
<212> DNA
<213> Homo sapiens
<400> 343
ccaaaaaaat caagatttaa ttttttatt tgcactgaaa aactaatcat aactgttaat 60
tctcaqccat ctttqaaqct tqaaaqaaqa qtctttggta ttttgtaaac gttagcagac 120
tttcctgcca gtgtcagaaa atcctattta tgaatcctgt cggtattcct tggtatctga 180
aaaaaatacc aaatagtacc atacatgagt tatttctaag tttgaaaaaat aaaaagaaat 240
tgcatcacac taattacaaa atacaagttc tggaaaaaat attttcttc attttaaaac 300
tttttttaac taataatggc tttgaaagaa gaggcttaat ttgggggtgg taactaaaat 360
caaaagaaat gattgacttg agggtctctg tttggtaaga atacatcatt agcttaaata 420
agcagcagaa ggttagtttt aattatgtag cttctgttaa tattaagtgt tttttgtctg 480
tittacctca atttgaacag ataagtttgc ctgcatgctg gacatgcctc agaaccatga 540
atagecegta etagatettg ggaacatgga tettagagte etttggaata agttettata 600
taaatacccc c
                                                                   611
<210> 344
<211> 311
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1, 275, 284, 296, 297, 300
<223> n = A, T, C or G
```

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<400> 344
nctegaaaaa geecaagaca geagaageag acaceteeag tgaactagea aagaaaagea 60
aagaagtatt cagaaaagag atgtcccagt tcatcgtcca gtgcctgaac ccttaccgga 120
aacctgactg caaagtggga agaattacca caactgaaga ctttaaacat ctggctcgca 180
agetgactea eggtgttatg aataaggage tgaagtactg taagaateet gaggacetgg 240
agtgcaatga gaatgtgaaa cacaaaacca aggantacat taanaagtac atgcannaan 300
tttggggctt g
<210> 345
<211> 201
<212> DNA
<213> Homo sapiens
<400> 345
cacacggtca tecegactge caacetggag geceaggeee tgtggaagga geegggeage 60
aatgtcacca tgagtgtgga tgctgagtgt gtgcccatgg tcagggacct tctcaggtac 120
ttctactccc gaaggattga catcaccctg tcgtcagtca agtgcttcca caagctggcc 180
tctgcctatg gggccaggca g
                                                                   201
<210> 346
<211> 370
<212> DNA
<213> Homo sapiens
<400> 346
ctgctccagg gcgtggtgtg ccttcgtggc ctctgcctcc tccgaggagc caggctgtgt 60
tctcttcaga atgttctgga gcagcagttt gaggegggtg atgcgttgga agggcagaat 120
cagaaaggac ttgagggaaa ggcgctggca gacggggtcg ctctccagct tctccaagac 180
ctcccggaaa ttgctgttgc tattcatcag gctctggaag gtgcgttcct gataggtctg 240
gttggtgaca taaggcaggt agacccggcg gaagtctggg gcgtggttca ggactacgtc 300
acatacttgg aaggagaaga tattgttctc aaagttctct tccaggtctg aaaggaacgt 360
ggcgctgacg
                                                                   370
<210> 347
<211> 416
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 416
<223> n = A, T, C or G
<400> 347
ctgttgtgct gtgtatggac gtgggcttta ccatgagtaa ctccattcct ggtatagaat 60
ccccatttga acaagcaaag aaggtgataa ccatgtttgt acagcgacag gtgtttgctg 120
agaacaagga tgagattgct ttagtcctgt ttggtacaga tggcactgac aatccccttt 180
ctggtgggga tcagtatcag aacatcacag tgcacagaca tctgatgcta ccagattttg 240
atttqctgga qqacattgaa agcaaaatcc aaccagqttc tcaacagqct qacttcctqq 300
atgcactaat cgtgagcatg gatgtgattc aacatgaaac aataggaaag aagtttggag 360
aagaggcata ttgaaatatt cactgacctc aagcagcccg attcagcaaa agtcan
<210> 348
<211> 351
<212> DNA
<213> Homo sapiens
<400> 348
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gtacaggaga ggatggcagg tgcagagcgg gcactgagct ctgcaggtga aagggctcgg 60
cagttggatg ctctcctgga ggctctgaaa ttgaaacggg caggaaatag tctggcagcc 120
tctacagcag aagaaacggc aggcagtgcc cagggacgag caggagacag atgccttcct 180
cttgtctcaa ctgcaaagag gcgttccttc ctctttcact aatcctcctc agcacagacc 240
ctttacgggt gtcaggctgg gggacagtaa ggtctttccc ttcccacaag gccatatctc 300
aggctgtctc agtgggggga aaccttggac aatacccggg ctttcttggg c
<210> 349
<211> 207
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 1
<223> n = A,T,C or G
<400> 349
nccgggacat ctccaccctc aacagtggca agaagagcct ggagactgaa cacaaggcct 60
tgaccagtga gattgcactg ctgcagtcca ggctgaagac agagggctct gatctgtgcg 120
acagagtgag cgaaatgcag aagctggatg cacaggtcaa ggagctggtg ctgaagtcgg 180
                                                                   207
cggtggaggc tgagcgcctg gtggctg
<210> 350
<211> 323
<212> DNA
<213> Homo sapiens
<400> 350
ccatacaggg ctgttgccca ggccctagag gtcattcctc gtaccctgat ccagaactgt 60
qqqqccaqca ccatccqtct acttacctcc cttcqqqcca aqcacaccca qqaqaactqt 120
gagacctggg gtgtaaatgg tgagacgggt actttggtgg acatgaagga actgggcata 180
tgggagccat tggctgtgaa gctgcagact tataagacag cagtggagac ggcagttctg 240
ctactgcgaa ttgatgacat cgtttcaggc cacgaaaaga aaggcgatga ccagagccgg 300
caaggcgggg ctcctgatgc tgg
<210> 351
<211> 353
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 12, \( \bar{2}5, \) 39, 42
<223> n = A, T, C or G
egeogeatee entgqteeet teeanteeet ttteetttnt engggaacgt gtatgeggtt 60
tqtttttqtt ttqtaqqqtt tttttccttc tccacctctc cctqtctctt ttqctccatg 120
ttgtccgttt ctgtggggtt aggtttatgt ttttaatcat ctgaggtcac gtctatttcc 180
teeggacteg cetgettggt ggegattete caceggttaa tatggtgegt eeettttte 240
ttttgttgcg aatctgagcc ttcttcctcc agcttctgcc ttttgaactt tgttcttcgg 300
ttctgaaacc atacttttac ctgagtttcc gtgaggctga ggctgtgtgc caa
<210> 352
<211> 467
<212> DNA
<213> Homo sapiens
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<400> 352		1				
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aactctggct ctactatccc tcacccaagc	ttcagtggag gctgggtagt tttaaccgca	agccatgcag gcattaaagt gcagttgagg gctatccctc	acagcatgaa ccatcaaagc cagagtccct	gacctcatct caactgttct gacccgtggg	gcagaaacac gataatgaat	300 360 420
	tagagcccgt	ttctatgctg	ttcaaaaact	ggcccga		467
<210> 353 <211> 350 <212> DNA <213> Homo	sapiens					
<400> 353						
gaaatctgtc gaaatgctgc ctgattgtgt gagttacaac	cccaccagga acgggaactg agttttcctg aggattctga	cctcccatgg acagcccctg cctcctggag gactgcattt ccatgaagtt	gaaaacggcc gaccagcttt caaattgact ctcttttagg	ccgtcctcta accttcccca caggaactgt taacagatcc	ccaccttgtg gacatttgtc ttattgcatg	120 180 240
ttgaagatgc	ttcagatcca	acaccaacaa	gggcaaaccc	ctttgactgg		350
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ataagaacag ctaccgctct gaggagg
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<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222>25, \overline{2}9
<223> n = A, T, C or G
<400> 357
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gtgcggccca cgccagcact gcagtgcacc gtgataggcc catcctgtcc aaactgctcc 120
ttggtcttat gcacctgccc gatgaagtca atgaatccct cgcctgtctt gggcacgccc 180
tgctctgg
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<211> 291
<212> DNA
<213> Homo sapiens
<400> 358
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cagggaattt cacaatgttc ttctatacaa tggctggaat ctatgaataa catcagtttc 240
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<210> 359
<211> 117
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 79, 98, 100
<223> n = A, T, C or G
<400> 359
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<210> 360
<211> 394
<212> DNA
<213> Homo sapiens
<400> 360
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aagtttgccc cagetttccc gggcacacca cettttgtcc caagtgtctg ccggtcgacc 180
aatctgcctg ccacacattg accaagccag acceggttca cccagctcga ggatcccagg 240
ttgaagagtg gccccttgag gccctggaaa gaccaatcac tggacttctt cccttgagag 300
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<210> 361
<211> 394
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> 28, 31
<223> n = A, T, C or G
<400> 361
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tgagtctgtg ggatagctgc catgaagtaa cctgaaggag gtgctggctg gtaggggttg 180
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tgaqcctggc gctcttcttt gcgctgagct aaagctacat acaatggctt tgtggacctc 300
ggccgcgacc acgctaagcc gaattccagc acactggcgg ccgttactag tggatccgag 360
ctcggtacca agcttggcgt aatcatggtc atag
<210> 362
<211> 268
<212> DNA
<213> Homo sapiens
<400> 362
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tgtttaagga tggtctcggt ggttaggccc actagaataa actgagtcca atacctctac 180
acagttatgt ttaactgggc tctctgacac cgggaggaag gtggcggggt ttaggtgttg 240
caaacttcaa tggttatgcg gggatgtt
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<210> 363
<211> 323
<212> DNA
<213> Homo sapiens '
<400> 363
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gtttgtaccc gttgatgata gaatggggta ctgatgcaac agttgggtag ccaatctgca 120
qacaqacact qqcaacattq cqqacaccct ccaqqaaqcq aqaatqcaqa gtttcctctg 180
tgatatcaaq cacttcaggg ttgtagatgc tgccattgtc gaacacctgc tggatgacca 240
gcccaaagga gaagggggag atgttgagca tgttcagcag cgtggcttcg ctggctccca 300
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<210> 364
<211> 393
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 29
<223> n = A,T,C or G
<400> 364
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ccagagtete egtgeagegg acteaggete eag
<210> 365
<211> 371
<212> DNA
<213> Homo sapiens
<400> 365
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ctcacaattc c
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<211> 393
<212> DNA
<213> Homo sapiens
<400> 366
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tggcaaccct tttttctqct gtcaqctqqa qaqaqatqac taccctqaqa atctcatcaa 180
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gcatgcccaa caggatggca agctcccgat tcctatcatc gatgatggga aaaggtaact 360
tttctgtggg ctcttcacaa ttgtaagcat tga
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<210> 367
<211> 327
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 34, 54, 55
<223> n = A, T, C or G
<400> 367
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gcagaacgat gcgggcattg tccacagtat ttgcgaaqat ctgagccctc aggtcctcga 120
tgatcttgaa gtaatggctc cagtctctga cctggggtcc cttcttctcc aagtgctccc 180
ggattttgct ctccagcctc cggttctcgg tctccaggct cctcactctg tccaggtaaq 240
aggecaggeg gtegtteagg etttgeatgg teteettete gttetggatg ceteceatte 300
ctgccagacc cccggctatc ccqqtqq
                                                                   327
<210> 368
<211> 306
<212> DNA
<213> Homo sapiens
<220>
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114

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<221> misc feature
<222> 24
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<400> 368
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aacggaggca ctgtggccga gaagctggac tgggcccgcg agaggcttga gcagcaggta 180
cctgtgaacc aagtgtttgg gcaggatgag atgategacg tcateggggt gaccaagggc 240
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cgagga
<210> 369
<211> 394
<212> DNA
<213> Homo sapiens
<400> 369
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eggetgeeac gaaagtgegt ttetttgtgt tetegggttg gaacegtgat ttecacagae 120
ccttgaaata cactgcgttg acgaggacca gtctggtgag cacaccatca ataagatctg 180
gggacagcag attgtcaatc atatccctgg tttcattttt aacccatgca ttgatggaat 240
cacaggeaga ggctggatcc tcaaagttca cattccggac ctcacactgg aacacatctt 300
tgttccttgt aacaaaagge acttcaattt cagaggeatt ettaacaaac aeggegttag 360
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                                                                  394
<210> 370
<211> 653
<212> DNA
<213> Homo sapiens
<400> 370
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ctggtgtcac agaggctact attactggcc tggaaccggg aaccgaatat acaatttatg 180
tcattgccct gaagaataat cagaagagcg agcccctgat tggaaggaaa aagacagacg 240
agetteecea aetggtaace ettecaeace ecaatettea tggaceagag atettggatg 300
tteetteeac agtteaaaag acceetteg teacceacce tgggtatgae actggaaatg 360
gtattcagct tcctggcact tctggtcagc aacccagtgt tgggcaacaa atgatctttg 420
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caagaccata cccgccgaat gtaggacaag aagctctctc tcagacaacc atctcatggg 540
ccccattcca qqacacttct qaqtacatca tttcatqtca tcctqttqqc actqatqaaq 600
aaccettaca qttcaqqqtt cetqqaactt ctaccaqtqc caetetqaca qqa
                                                                  653
<210> 371
<211> 268
<212> DNA
<213> Homo sapiens
<400> 371
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etetteetge eacttetttg ecacaaagtg caccetggag ggeaccaaga agggeeacaa 120
gctccacctg gactacatcg ggccttgcaa atacatcccc ccttgcctgg actctgagct 180
gaccgaatte eccetgegea tgegggaetg geteaagaac gteetggtea ecctgtatga 240
qaqqqatqaq qacaacaacc ttctqact
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<210> 372
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<211> 392

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<212> DNA
<213> Homo sapiens
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ggtgctgctg gtactcctgg tctgcaagga atgcctggag aaagaggagg tcttggaagt 180
cctggtccaa agggtgacaa gggtgaacca ggcggtccag gtgctgatgg tgtcccaggg 240
aaagatggcc caaggggtcc tactggtcct attggtcctc ctggcccagc tggccagcct 300
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cctggtgaga gaggtgaaac ctcggccgcg ac
<210> 373
<211> 388
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 30
<223> n = A, T, C or G
<400> 373
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gccaagetee ceagteatee tggteaaagg gatettegat agacaceaet gggtagteet 360
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<210> 374
<211> 393
<212> DNA
<213> Homo sapiens
<400> 374
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aagggttgga tgggctgtct gagcgctgtg cccagtacaa gaaggacgga gctgacttcg 240
ccaagtggcg ttgtgtgctg aagattgggg aacacaccc ctcagccctc gccatcatgg 300
aaaatgccaa tgttctggcc cgttatgcca gtatctgcca gcagaatggc attgtgccca 360
tcgtggagcc tgagatcctc cctgatgggg acc
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<210> 375
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222>30, \overline{3}3
<223> n = A, T, C or G
<400> 375
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aggaaagagg ggatgaactt gcagactctg cgcttgagat cttcaaacaa qcatcagcqt 120
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tttccagggc ttcccagagg tctgtgcgac tagcccctgt ctatcaaaag ttattagaga 180
ggatgaagca ttagcttgaa gcactacagg aggaatgcac cacggcagct ctccgccaat 240
ttctctcaga tttccacaga gactgtttga atgttttcaa aaccaagtat cacactttaa 300
tgtacatggg ccgcaccata atgagatgtg agccttgtgc atgtggggga ggagggagag 360
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<210> 376
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30
<223> n = A, T, C or G
<400> 376
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ctettectgc cacttetttg ccacaaagtg caccetggag ggcaccaaga agggccacaa 120
getecacetg gaetacateg ggeettgeaa atacateece eettgeetgg actetgaget 180
gaccgaattc cccctgcgca tgcgggactg gctcaagaac gtcctggtca ccctgtatga 240
qaqqqatqaq qacaacaacc ttctqactqa qaaqcaqaaq ctqcqqqtqa aqaaqatcca 300
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cgagaagaac tataacatgt acatcttccc tg
<210> 377
<211> 292
<212> DNA
<213> Homo sapiens
<400> 377
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agacttggct ccaccactga tatcctcctt tggggaaagg cttggcacac agcaggcttt 240
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<210> 378
<211> 395
<212> DNA
<213> Homo sapiens
<400> 378
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agcagtatca atgtctctgc tgattgcact ggtctgaaac tccctttgga ttagctgaga 180
cacaccattc tgggccctga ttttcctaag atagaactcc aactctttgc cctctagcac 240
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<210> 379
<211> 223
<212> DNA
<213> Homo sapiens
<400> 379
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agetecagee accaecagge tgageagtga ggagagaaag tttetgeetg geeetgeate 120
tggttccagc ccacctgccc tccccttttt cgggactctg tattccctct tgggctgacc 180
acagettete cettteceaa ecaataaagt aaceaettte age
<210> 380
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222>30,\overline{3}2
<223> n = A, T, C or G
<400> 380
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attccgcagg ggccctcctc gccaaagaca gcctagagag gacggcaatg aagaagataa 180
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<210> 381
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 29, \overline{3}0, 31
<223> n = A, T, C or G
<400> 381
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<210> 382
<211> 234
<212> DNA
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ccgcgacttc gttcaggtac atgaagagct ccaaggaggt ctggtgggtg gtgccatcct 180
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<210> 383
<211> 396
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 66
\langle 223 \rangle n = A,T,C or G
<400> 383
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gtttgnaccc gttgatgata gaatggggta ctgatgcaac aqttgggtag ccaatctgca 120
gacagacact ggcaacattg cggacaccca ggatttcaat ggtgcccctg gagattttag 180
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<210> 384
<211> 396
<212> DNA
<213> Homo sapiens
<400> 384
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<210> 385
<211> 2943
<212> DNA
<213> Homo sapiens
<400> 385
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gacageetet ttgtcaatgg tttcaeteat eggagetetg tgtccaecae eagcaeteet 660
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attecacaaa ttaagetgta qtatqtaccc taagacgetg ctaattgact gccacttegc 1440
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aaaggtgeet tggettetet teecaaetga caaatgeeaa agttgagaaa aatgateata 1560
attttagcat aaacagagca gtcggcgaca ccgattttat aaataaactg agcaccttct 1620
ttttaaacaa acaaatgcgg gtttatttct cagatgatgt tcatccgtga atggtccagg 1680
gaaggacett teacettgae tatatggeat tatgteatea eaagetetga ggetteteet 1740
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caqctgggt gatttcgccc cccatctccg ggggaatgtc tgaagacaat tttggttacc 1860
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tgtcaactgt gtcaggacta agaaaccctg gttttgagta gaaaagggcc tggaaagagg 2040
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gagettetaa gtttettee etteatteta eeetgeaage caagttetgt aagagaaatg 2280
cctgagttct agctcaggtt ttcttactct gaatttagat ctccagaccc ttcctggcca 2340
caattcaaat taaggcaaca aacatatacc ttccatgaag cacacacaga cttttgaaag 2400
caaggacaat gactgcttga attgaggcct tgaggaatga agctttgaag gaaaagaata 2460
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<210> 392
<211> 309
<212> PRT
<213> Homo sapiens
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His Ala Ser Ala His Ala Ser Gly Arg Gln Arg Gln Leu His Ser Ala
Ser Thr Gln Ile Arg Trp Glu Pro Ser Pro Ala Met Ala Ser Leu Gly
                                25
Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile Ile Leu Ala Gly
                            40
Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser Gly Arg His Ser Ile
                                            60
                        55
Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile Gly Glu Asp Gly Ile
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70
                                      75
65
Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu Ser Asp Ile Val Ile
                                  90
              85
Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val His Glu Phe Lys Glu
                              105
          100
Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met Phe Arg Gly Arg Thr
                          120
Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn Ala Ser Leu Arg Leu
                      135
                                          140
Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr Lys Cys Tyr Ile Ile
                   150
                                      155
Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala
                                  170
Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr
          180
                              185
Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp
                          200
Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr
                    215
                                          220
Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met Lys Val Val Ser Val
                  230
                                      235
Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser Cys Met Ile Glu Asn
Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val Thr Glu Ser Glu Ile
                             265
Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser Lys Ala Ser Leu Cys
               280
Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu Leu Pro Leu Ser Pro
Tyr Leu Met Leu Lys
305
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<210> 393

<211> 282

<212> PRT

<213> Homo sapiens

<400> 393

Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser 25 Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile • 40 Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu 55 Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val 75 His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn 105 Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr 120 Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu 135

Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn

150 155 Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln 165 170 Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser 185 Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met 200 Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser 215 Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val 230 235 Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser 245 250 Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu 260 265 270 Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys <210> 394 <211> 20 <212> PRT <213> Homo sapiens <400> 394 Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile 10 Ile Ile Leu Ala 20 <210> 395 <211> 20 <212> PRT <213> Homo sapiens <400> 395 Ile Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile 1 Ser Gly Arg His 20 <210> 396 <211> 20 <212> PRT <213> Homo sapiens <400> 396 Ile Ser Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly 1 Asn Ile Gly Glu 20 <210> 397 <211> 20 <212> PRT

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Gly Asn Ile Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp
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Ile Lys Leu Ser
<210> 398
<211> 20
<212> PRT
<213> Homo sapiens
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Asp Ile Lys Leu Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val
1
                                    10
Leu Gly Leu Val
<210> 399
<211> 20
<212> PRT
<213> Homo sapiens
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Val Leu Gly Leu Val His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser
Glu Gln Asp Glu
<210> 400
<211> 20
<212> PRT
<213> Homo sapiens
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Ser Glu Gln Asp Glu Met Phe Arg Gly Arg Thr Ala Val Phe Ala Asp
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Gln Val Ile Val
            20
<210> 401
<211> 20
<212> PRT
<213> Homo sapiens
<400> 401
Asp Gln Val Ile Val Gly Asn Ala Ser Leu Arg Leu Lys Asn Val Gln
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Leu Thr Asp Ala
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<210> 402

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<211> .21
<212> PRT
<213> Homo sapiens
<400> 402
Val Gln Leu Thr Asp Ala Gly Thr Tyr Lys Cys Tyr Ile Ile Thr Ser
Lys Gly Lys Gly Asn
            20
<210> 403
<211> 20
<212> PRT
<213> Homo sapiens
<400> 403
Lys Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala Phe Ser
Met Pro Glu Val
            20
<210> 404
<211> 20
<212> PRT
<213> Homo sapiens
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Ser Met Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr Leu
Arg Cys Glu Ala
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<210> 405
<211> 20
<212> PRT
<213> Homo sapiens
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Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp
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Ala Ser Gln Val
            20
<210> 406
<211> 20
<212> PRT
<213> Homo sapiens
<400> 406
Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn
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Thr Ser Phe Glu
            20
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<211> 20
<212> PRT
<213> Homo sapiens
<400> 407
Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met Lys Val Val
1
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Ser Val Leu Tyr
    . 20
<210> 408
<211> 20
<212> PRT
<213> Homo sapiens
<400> 408
Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser Cys Met
                           10
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Ile Glu Asn Asp
<210> 409
<211> 20
<212> PRT
<213> Homo sapiens
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Met 'Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val Thr
Glu Ser Glu Ile
           20
<210> 410
<211> 20
<212> PRT
<213> Homo sapiens
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Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
1
Lys Ala Ser Leu
           20
<210> 411
<211> 20
<212> PRT
<213> Homo sapiens
Ser Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala
1
Leu Leu Pro Leu
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132

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<213> Homo sapiens
<400> 412
Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu Leu Pro Leu Ser Pro Tyr
1 5
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Leu Met Leu Lys
<210> 413
<211> 35
<212> PRT
<213> Homo sapiens
<400> 413
Ile Ser Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly
          5
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Asn Ile Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile
Lys Leu Ser
<210> 414
<211> 35
<212> PRT
<213> Homo sapiens
<400> 414
Val Leu Gly Leu Val His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser
1 5
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Glu Gln Asp Glu Met Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln
                             25
Val Ile Val
       35
<210> 415
<211> 65
<212> PRT
<213> Homo sapiens
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Lys Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala Phe Ser
1 5
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Met Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr Leu Arg
          20
                             25
Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp Ala Ser
                       40
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Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr Ser Phe
50 . 55
Glu
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65

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Lys Leu Ser Asp Ile Val Ile Gln Trp Leu 1 5 10
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Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile
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Leu Leu Asn Ser Lys Ala Ser Leu Cys Val
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Ser Leu Cys Val Ser Ser Phe Phe Ala Ile
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Val Leu Tyr Asn Val Thr Ile Asn Asn Thr
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<213> Homo sapiens

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Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
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<211> 10
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<213> Homo sapiens
<400> 422
Leu Leu Pro Leu Ser Pro Tyr Leu Met Leu
1 5
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<211> 10
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<213> Homo sapiens
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Cys Meť Ile Glu Asn Asp Ile Ala Lys Ala
       5
<210> 424
<211> 10
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<213> Homo sapiens
<400> 424
Lys Thr Gly Ala Phe Ser Met Pro Glu Val
     5
<210> 425
<211> 10
<212> PRT
<213> Homo sapiens
<400> 425
Trp Ala Leu Leu Pro Leu Ser Pro Tyr Leu
1
          5
<210> 426
<211> 10
<212> PRT
<213> Homo sapiens
<400> 426
Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile
1 5
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<213> Homo sapiens

<400> 427

Gin Leu Thr Asp Ala Gly Thr Tyr Lys Cys

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<211> 10

<212> PRT

<213> Homo sapiens

<400> 428

Ala Leu Leu Pro Leu Ser Pro Tyr Leu Met
1 5 10

<210> 429

<211> 10

<212> PRT

<213> Homo sapiens

<400> 429

Gln Leu Leu Asn Ser Lys Ala Ser Leu Cys 1 5 10

<210> 430

<211> 10

<212> PRT

<213> Homo sapiens

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Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile
1 5 10

<210> 431

<211> 10

<212> PRT

<213> Homo sapiens

<400> 431

Trp Leu Lys Glu Gly Val Leu Gly Leu Val 1 5 10

<210> 432

<211> 10

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Z4005 432

Leu Gln Leu Leu Asn Ser Lys Ala Ser Leu 1 5 10

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Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile
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Gly Ile Ser Gly Arg His Ser Ile Thr Val
<210> 435
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Phe Glu Pro Asp Ile Lys Leu Ser Asp Ile
1 5
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<211> 9
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Ala Leu Leu Pro Leu Ser Pro Tyr Leu
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Ser Leu Cys Val Ser Ser Phe Phe Ala
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Ile Leu Phe Trp Ser Ile Ile Ser Ile
1
      5
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Gln Leu Leu Asn Ser Lys Ala Ser Leu
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Lys Val Val Ser Val Leu Tyr Asn Val
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Ile Leu Ala Gly Ala Ile Ala Leu Ile
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Trp Leu Lys Glu Gly Val Leu Gly Leu
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Ile Ile Leu Ala Gly Ala Ile Ala Leu
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Asn Val Thr Met Lys Val Val Ser Val
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Glu Met Phe Arg Gly Arg Thr Ala Val
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Ala Val Phe Ala Asp Gln Val Ile Val
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Leu Leu Pro Leu Ser Pro Tyr Leu Met
1 5
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Leu Leu Asn Ser Lys Ala Ser Leu Cys
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Val Ile Gln Trp Leu Lys Glu Gly Val
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Ser Leu Gly Gln Ile Leu Phe Trp Ser
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Ile Ala Leu Ile Ile Gly Phe Gly Ile
1 5
<210> 453
<211> 9
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<213> Homo sapiens
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Cys Thr Phe Glu Pro Asp Ile Lys Leu
1
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Ile Val Gly Asn Ala Ser Leu Arg Leu
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Gly Gln Ile Leu Phe Trp Ser Ile Ile
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## <213> Homo sapiens

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var	val	ser	GTU	565	Pro	Phe	Inr	ren	570	Pne	Tnr	тте	Asn		Leu
7	<b></b>					<b>~</b> 3 ···	<b>~</b> 3 -	_		_	-	-		575	~
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Thr Ser Val 625 Gln Leu Asp	Asp Leu 610 Lys Pro Ser Lys	Asn 595 Gly Asn Leu Gln Asp 675	580 Val Ala Gly Ser Gln 660 Ser	Asp Met Arg Ala Gly 645 Thr	Lys Tyr Glu 630 Pro His	Thr 615 Thr Gly Gly Leu	Leu 600 Gly Arg Leu Ile Asn 680	585 Leu Cys Val Pro Thr 665 Gly	Gly Ser Arg Asp Ile 650 Arg	Pro Val Leu 635 Lys Leu Asn	Leu Ile 620 Leu Gln Gly Glu	Phe 605 Ala Cys Val Pro Pro 685	590 Gln Leu Thr Phe Tyr 670 Gly	Asn Arg Arg Tyr His 655 Ser Leu	Ser Ser Leu 640 Glu Leu Asp
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Ala Pro Gly Ser Ser Thr Pro Arg Arg Gly Ser Phe Arg Ala Trp Ser
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Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala
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Ile Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu
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His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val
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 Pro
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 Asp
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 Asp
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 Lys
 Ser
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 Gly
 Leu
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 Asp
 Arg
 His
 Arg
 His

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<211> 210

225

<212> PRT

<213> Homo sapiens

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<210> 482

<211> 97

<212> PRT

<213> Homo sapiens

<400> 482

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 Met
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 Ser
 His
 Ser
 Gly
 Ala
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 Cys
 Pro
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 Leu
 Ala
 Phe
 Leu
 Ala
 Phe
 Leu
 Ala
 Phe
 Leu
 Ala
 Leu
 Blu
 His
 Leu
 Gly
 Leu
 Gln
 Phe
 Leu

 Asn
 Leu
 Val
 Pro
 Arg
 Leu
 Pro
 Ala
 Leu
 Ser
 Trp
 Cys
 Tyr
 Ser
 Leu
 Ser

 Thr
 Ser
 Pro
 Thr
 Cys
 Gly
 Met
 Arg
 Arg
 Arg
 Ala
 Cys
 Ser
 Thr
 Leu
 Ser
 Fro
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 Arg
 Ala
 Leu
 Arg
 Ala
 Leu
 Ala
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 Ala
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Asp

<210> 483

<211> 438

<212> PRT

<213> Homo sapiens

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Thr	Glu	Gly 35	Val	Leu	Gln	His	Leu 40	Leu	Arg	Pro	Leu	Phe 45	Gln	Lys	Ser
	50				_	Leu 55	-	_			60			_	
65					70	Thr			_	75		_		_	80
				85		Gly			90				_	95	
			100			Gly		105					110		
_	_	115				Ile	120		_			125			
тте	Arg 130	СТĀ	GLu	Tyr	GIN	Ile 135	Asn	Phe	His	Ile	Val 140	Asn	Trp	Asn	Leu
Ser 145	Asn	Pro	Asp	Pro	Thr 150	Ser	Ser	Glu	Tyr	Ile 155	Thr	Leu	Leu	Arg	Asp 160
				165		Thr		_	170	_				175	
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		195				Phe	200					205			
	210					Lys 215					220				
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		275				Arg	280					285			
	290			-		Ser 295			_		300			_	_
305					310	Ser				315				-	320
-			-	325		Ser			330	_	_		-	335	
			340			Leu		345					350		
		355			_	Arg	360					365			
	370					Leu 375					380				
385					390	Leu				395					400
				405		Val			410		-			415	
			420			Gln	Суѕ	Pro 425	Gly	Tyr	Tyr	Gln	Ser 430	His	Leu
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Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro

Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Lys 120 Leu Thr Asn Asp Ile Glu Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 135 140 Ser Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr 150 155 Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Arg Thr Ser Val Asp Ser 170 Ile Leu Pro Leu Gln Pro His Asn Tyr Gly Cys Trp Pro Ser Pro Gly 185 Thr Ile His Pro Gln Leu His His His Gln Pro Ala Val Trp Gly Gly 200 His Gly Ser Pro Trp Leu Gln Glu Val Gln His His Arg Glu Gly Pro 215 220 Ala Gly Ser Ala Trp Ser His Ile Gln Glu His Gln Cys Trp Pro Ser 230 235 Val Leu Trp Leu Gln Thr Asp Leu Ser Gln Val Gln Glu Gly Trp Ser 245 250 Ser His Trp Ser Gly Cys His Leu His Pro Ser Ser

<210> 486

<211> 304

<212> PRT

<213> Homo sapiens

<400> 486

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Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Pro Lys 250

Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr 260

Leu Asn Ser His Leu Gln Ser Pro Val Pro Thr Arg Tyr Gly Gln Gly 275

Leu Lys Val His Ser IIe His Arg Gly Gly Ser Pro Ser 300

Lys Val His Ser IIe His Arg Gly Gly Ser Pro Ser 300

<210> 487 <211> 294

<212> PRT

<213> Homo sapiens

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<210> 488

<211> 233

167

<212> PRT <213> Homo sapiens

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Ser His Leu Asp Leu Glu Asp Leu Gln

<210> 489 <211> 178 <212> PRT

225

<213> Homo sapiens

<400> 489

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 Gln
 Val
 Phe
 Leu
 Asp
 Lys
 Thr
 Leu
 Asn
 Ala
 Ser
 Phe

 His
 Trp
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 Gly
 Ser
 Thr
 Tyr
 Gln
 Leu
 Val
 Asp
 Ile
 His
 Val
 Thr
 Glu
 Glu
 25
 Ser
 Ser
 Ser
 Fun
 Glu
 Asn
 Fun
 Thr
 Glu
 Fun
 Thr
 Glu
 Fun
 Thr
 Fun
 Fu

Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly 130 135 140 Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp 150 155 Gly Tyr Phe Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe <210> 490 <211> 15 <212> PRT <213> Homo sapiens <400> 490 Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu Ala Pro Gly Ser 5 <210> 491 <211> 15 <212> PRT <213> Homo sapiens <400> 491 Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr <210> 492 <211> 15 <212> PRT <213> Homo sapiens <400> 492 Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro 5 <210> 493 <211> 15 <212> PRT <213> Homo sapiens <400> 493 Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu 1 <210> 494 <211> 15 <212> PRT <213> Homo sapiens <400> 494 Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr 10

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Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile
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Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu
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Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser
<210> 500
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Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr
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Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu
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acttcaccat ctccaatctc cagtattcac cagatatggg caagggctca gctacattca 180
actocaccga gggggtcctt cagcacctgc tcagaccett gttccagaag agcagcatgg 240
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ctggtgtgga caccacctgc acctaccacc ctgaccctgt gggccccggg ctggacatac 360
agcagettta etgggagetg agteagetga eccatggtgt cacecaactg ggettetatg 420
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<213> Homo sapiens
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teacactgaa etteaceate aacaacetge getacatgge ggacatggge caaceegget 120
ccctcaagtt caacatcaca gacaacgtca tgaagcacct gctcagtcct ttgttccaga 180
ggagcagcct gggtgcacgg tacacaggct gcagggtcat cgcactaagg tctgtgaaga 240
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gtctgcctat caagcaggtg ttccatgagc tgagccagca gacccatggc atcacccggc 360
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aggetqqaca qaqaqcaqet qtattqqqaq etqaqecaqe tqacccacaa tatcactqaq 420
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ctggctccag gaagttcaac accacggaga gggtccttca gggcctgctc aggtccctgt 240
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tgctattcac aattaacttc accatcacta acctgcggta tgaggagaac atgcatcacc 180
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<210> 522
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tactetggtt geagactgac ettgeteagg cetgagaagg atggggeage caccagagtg 120
gatgetgtet geacceateg teetgaceee aaaageeetg gactggacag agageggetg 180
tactggaage tgagecaget gaccaegge atcactgage tgggeceeta caccetggae 240
aggcacagtc tctatgtcaa tg
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<213> Homo sapiens
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teteteteag gtetgagaag gatggggcag ceaetggagt ggatgccate tgeaeceaec 180
accttaaccc tcaaagcctg gactggacag ggagcagctg tactggcagc tgagccagat 240
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cccttaactg ggaattetga ccttcccttc tgggctgtca tcytcatcgg cttggcagga 10380
ctcctgggac tcatcacatg cctgatctgc ggtgtcctgg tgaccacccg ccggcggaag 10440
aaggaaggag aatacaacgt ccagcaacag tgcccaggct actaccagtc acacctagac 10500
ctggaggatc tgcaatgact ggaacttgcc ggtgcctggg gtgcctttcc cccagccagg 10560
<210> 570
<211> 469
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 71,92,93,120,124,168,178,218,230,300,
      321, 350, 387, 412, 414, 415, 422, 423, 451
\langle 223 \rangle n = A,T,C or G
<400> 570
gttteaccea teggagetet gtgeecacea ceageactee tgggaeetee acagtggaee 60
tgggaacete wgggaeteca tectecetee cyrgececae agetgetgge ceteteetgr 120
tgcyattcac cctcaacttc accatcacca acctgcagta tgaggagrac atgcatcrcc 180
ctggctccag gaagttcaac accacggaga gggtcctkca gggtctgcty aggtcccttg 240
ttcaagaaca ccagtgttgg ccctctgtac tctggctgca gactgacctt gctcaggccy 300
gagaaggatg gggcagccac yggagtggat gccatctgca cccaccgccy tgaccccaaa 360
agccctggac tggacagaga gcagctrtac tgggagctga gccagctgac cmayrgcatc 420
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<210> 571
<211> 130
<212> PRT
<213> Homo sapiens
<220>
<221> variant
<222> 69,107,110
<223> Xaa = Any amino acid
<400> .571
His Pro Gln Leu Glu Gln Gln Pro Gln Ser His Ser Trp Cys His Ser
                                    10
Pro Ser Thr Ser Thr His His Gln Pro Ala Val Arg Gly Gly His Ala
            20
                                25
                                                    30
```

Ala Pro Gly Ser Arg Lys Phe Asn Ala His Arg Glu Arg Thr Ala Gly
35 40 45

Ser Cys Ser Asn Pro Arg Ser Gly Ile Ala Val Trp Asn Thr Ser Ile 50 55 60

Gln Ala Ala Asp Xaa Pro His Ser Gly Gln Arg Arg Ile Ala Gln Pro 65 70 75 80

Arg Gln Trp Met Pro Ser Ala His Ile Ala Leu Thr Leu Lys Thr Ser 85 90 95

Asp Trp Thr Glu Ser Asp Cys Thr Gly Ser Xaa Ala Ile Xaa Gln Met 100 105 110

Ala Ser Arg Ser Trp Ala Pro Thr Pro Trp Thr Gly Thr Val Ser Met 115 120 125

Ser Met 130

<210> 572

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 1,58,78,92,94

<223> Xaa = Any amino acid

<400> 572

Xaa Ile Pro Ser Ser Asn Ser Ser His Ser Pro Ile His Gly Ala Ile 5 10 15

His Pro Gln Leu Gln Leu Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met
20 25 30

Arg His Leu Val Pro Gly Ser Ser Thr Arg Thr Glu Arg Glu Leu Gln 35 40 . 45

Gly Arg Ala Gln Thr Leu Asp Gln Glu Xaa Gln Ser Gly Ile Pro Leu 50 55. 60

Phe Arg Leu Gln Thr Ser Leu Thr Gln Ala Arg Glu Gly Xaa Leu Ser 65 70 75 80

His Gly Ser Gly Cys His Leu His Thr Ser Pro Xaa Pro Xaa Arg Pro 85 90 95

Arg Thr Gly Gln Arg Ala Thr Val Leu Gly Ala Glu Gln Ser Asp Lys 100 105 110

Trp His Pro Gly Ala Gly Pro Leu His Pro Gly Pro Glu Gln Ser Leu 115 120 125

Cys Gln

191

130

<210> 573

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 1,54

<223> Xaa = Any amino acid

<400> 573

Xaa Ser Pro Ala Arg Thr Ala Ala Thr Val Pro Phe Met Val Pro Phe
5 10 15

Thr Leu Asn Phe Asn Ser Ser Pro Thr Cys Ser Thr Arg Arg Thr Cys
20 25 30

Gly Thr Trp Phe Gln Glu Val Gln Arg Ala Gln Arg Glu Asn Cys Arg 35 40 45

Val Val Leu Lys Pro Xaa Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr 50 55 60

Ser Gly Cys Arg Leu Ala Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala 65 70 75 80

Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu 85 90 95

Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn 100 105 110

Gly Ile Gln Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr 115 120 125

Val Asn 130

<210> 574

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 101

<223> Xaa = Any amino acid

<400> 574

Gly Phe Thr His Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val Asp Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser 20 25 30

192

Pro Thr Thr Ala Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg
50 55 60

Lys Phe Asn Thr Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 575

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 103

<223> Xaa = Any amino acid

<400> 575

Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val Asp Leu Arg Thr Ser Val Thr Pro Ser Ser Leu Ser Ser 20 25 30

Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 35 40 45

Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro Gly 50 55 60

Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly 65 70 75 80

Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 85 90 . 95

Leu Thr Ser Leu Arg Ser Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp 100 105 110

Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg 115 120 125

Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu 130 135 140

Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 576

<211> 122

<212> PRT

<213> Homo sapiens

<400> 576

Ala Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr

Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe 20 25 30

Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Arg Gly Pro Met Phe Lys
35 40 45

Asn Thr Ser Gly Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 50 55 . 60

Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr 65 70 75 80

His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr 85 90 95

Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr 100 105 110

Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 115 120

<210> 577

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 11,106,151

<223> Xaa = Any amino acid

<400> 577

Gly Phe Thr His Arg Thr Ser Val Pro Thr Xaa Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Phe Ser Leu Pro Ser 20 25 30

194

Pro Ala Thr Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 40

Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Leu Gly Pro Met

Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr

Leu Leu Arg Ser Glu Lys Asp Gly Ala Xaa Thr Gly Val Asp Ala Ile 100

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln 120

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Asn

<210> 578

<211> 155

<212> PRT

<213> Homo sapiens

<400> 578

Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr

Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro

Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile

Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe

Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu

Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys

Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu 120

Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro 130 135

195

Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 145 150 155

<210> 579

<211> 155

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 52,138

<223> Xaa = Any amino acid

<400> 579

Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro 20 25 30

Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile 35 40 45

Thr Asn Leu Xaa Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys 50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly Pro Met Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys 100 105 110

Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu 115 120 125

Tyr Trp Glu Leu Ser Gln Leu Thr Asn Xaa Ile Lys Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Ser Asn Ser Leu Tyr Val Asn 145 150 155

<210> 580

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 23

<223> Xaa = Any amino acid

<400> 580

Gly Phe Thr His Gln Thr Ser Ala Pro Asn Thr Ser Thr Pro Gly Thr

196

5 10 15

Ser Thr Val Asp Leu Gly Xaa Ser Gly Thr Pro Ser Ser Leu Pro Ser 20 25 30

Pro Thr Ser Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile 100 105 110

Cys Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 581

<211> 156

<212> PRT

<213> Homo sapiens

<400> 581

Gly Phe Thr His Arg Ser Ser Val Ala Pro Thr Ser Thr Pro Gly Thr

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser 20 25 30

Pro Thr Thr Ala Val Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Arg His Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu 65 70 75 80

Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Ile 85 90 95

Ser Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His His Leu Asn Pro Gln Ser Pro Gly Leu Asp Arg Glu Gln

197

115 120 125

Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 582

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 151

<223> Xaa = Any amino acid

<400> 582

Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr 5 10 15

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser 20 25 30

Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg
50 55 60

Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro Ile 65 70 75 80

Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala Val 100 105 110

Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Ser Leu Asp Arg Xaa Ser Leu Tyr Val Asn 145 150 155

<210> 583

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 109,114,117,128,139 <223> Xaa = Any amino acid

<400> 583

Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro Gly 20 25 30

His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe Thr 35 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Thr Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Gln Glu Ala Ala Thr Gly Xaa Asp Thr Ile 100 105 110

Cys Xaa His Arg Xaa Asp Pro Ile Gly Pro Gly Leu Asp Arg Glu Xaa 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Xaa Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150

<210> 584

<211> 156

<212> PRT

<213> Homo sapiens

<400> 584

Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr

Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser Leu Pro Gly 20 25 30

His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu Asn Phe Thr 35  $\cdot$  40  $\cdot$  45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr Leu Arg Leu Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Ser Val Thr Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 585

<211> 156

<212> PRT

<213> Homo sapiens

<400> 585

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr
5 10 15

Ser Ala Val His Leu Glu Thr Ser Gly Thr Pro Ala Ser Leu Pro Gly 20 25 30

His Thr Ala Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Arg Gly Ala Ala Thr Gly Val Asp Thr Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Leu Asn Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Cys Gly Ile Ile Glu Leu Gly 130 135 140

Pro Tyr Leu Leu Asp Arg Gly Ser Leu Tyr Val Asn 145 150 155

<210> 586

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 151,156 <223> Xaa = Any amino acid

<400> 586

Gly Phe Thr His Arg Asn Phe Val Pro Ile Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val His Leu Gly Thr Ser Glu Thr Pro Ser Ser Leu Pro Arg 20 25 30

Pro Ile Val Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Ala Met Arg His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Ile Gly Pro Leu Tyr Ser Ser Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Lys Ala Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Gln Ser Pro Gly Leu Asn Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Xaa 145 150 155

<210> 587

<211> 156

<212> PRT

<213> Homo sapiens

<400> 587

Gly Phe Thr His Trp Ser Pro Ile Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Ile Val Asn Leu Gly Thr Ser Gly Ile Pro Pro Ser Leu Pro Glu 20 25 30

Thr Thr Ala Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asn Met Gly His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ile Pro Gly Leu Asp Arg Gln Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 588

<211> 156

<212> PRT

<213> Homo sapiens

<400> 588

Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Phe Thr Val Gln Pro Glu Thr Ser Glu Thr Pro Ser Ser Leu Pro Gly
20 25 30

Pro Thr Ala Thr Gly Pro Val Leu Leu Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Ile Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg
50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Met Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 145 150 155

<210> 589

<211> 156

<212> PRT

<213> Homo sapiens

<400> 589

Gly Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr

.

10 15 Ser Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg 55 Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 150 <210> 590 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 145 <223> Xaa = Any amino acid <400> 590 Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 40 Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg 55 Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr

WO 02/06317 PCT/US01/22635

Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

<210> 591

<211> 155

<212> PRT

<213> Homo sapiens

<400> 591

Gly Phe Thr His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr
5 10 15

Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly 20 25 30

Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys 50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys 100 105 110

Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu 115 120 125

Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 592

<211> 134

<212> PRT

<213> Homo sapiens

<400> 592

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val

10 15 Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser 105 Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn 130 <210> 593 <211> 150 <212> PRT <213> Homo sapiens <220> <221> variant <222> 7 <223> Xaa = Any amino acid <400> 593 Gly Tyr Asn Glu Pro Gly Xaa Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp

105

Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser 115 120 125

Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg 130 135 140

Asp Ser Leu Phe Ile Asn 145 150

<210> 594

<211> 318

<212> PRT

· <213> Homo sapiens

<220>

<221> variant

<222> 136,248,268

<223> Xaa = Any amino acid

<400> 594

Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn 5 10

Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser 20 25 30

Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu 35 40 45

Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr 50 55 60

Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser 65 70 75 80

Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr 85 90 95

Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp 100 105 110

Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser 115 120 125

Ser Ser Thr Gln His Phe Tyr Xaa Asn Phe Thr Ile Thr Asn Leu Pro 130 135 140

Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn 145 150 155 160

Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser 165 170 175

Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val 180 185 190

Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro 200 Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg 215 Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Xaa Pro Asn Arg Asn Glu Pro Leu Thr 250 Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Xaa Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr 280 Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 310 <210> 595 <211> 3451 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> 177, 335, 523, 618, 663, 875, 961, 1001, 1441, 1555, 1560, 1563, 1574, 1585, 2065, 2070, 2683, 2990, 3269, 3381, 3401 <223> Xaa = Any Amino Acid <400> 595 Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr Ser Gly Cys Arg Leu Ala 5 1 10 Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala Thr Ala Val Asp Ala Ile

25 Cys Thr His Arg Pro Asp Pro Glu Asp Leu Gly Leu Asp Arg Glu Arg 40 Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn Gly Ile Gln Glu Leu Gly 55 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His 70 75 Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr Ser Thr Val Asp 85 90 Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala 105 Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu 120 Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr 135 140 Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr 150 155 Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro

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٧	T	7	C1	165	71-	mb	C1	17 T	170	21-	<b>T1</b> -	0	mъ	175	<b>7</b>
Add	гÀЗ	Asp	180	нта	АТа	THE	сту		Asp	ATS	тте	Суѕ		HIS	Arg
Ton	7 cm	Dro	_	Ca-	D×a	C1	Ton	185	71	C1	C1~	Leu	190	T	C1
пeп	тэр	195	пуз	SET	FIO	GTĀ	200	usii	ALY	GIU	GTH	205	TÄT	тър	GIU
T.e.ii	Ser		T.em	Thr	Aen	Zen		Glu	Glu	T.em	Gl v	Pro	ጥኒተ	ጥ ኮ ጉ	Lon
Дец	210	шуз	пса	1111	TWII	215	110	Gru	Gru	пеп	220	110	TYT	1117	Dea
Asp		Asn	Ser	Len	Tvr		Asn	Glv	Phe	Thr		Gln	Ser	Ser	Va1
225	9				230			3		235		<b>4</b>			240
	Thr	Thr	Ser	Thr		Glv	Thr	Ser	Thr	-	Asp	Leu	Ara	Thr	
				245		3			250		<u>F</u>		5	255	
Val	Thr	Pro	Ser	Ser	Leu	Ser	Ser	Pro		Ile	Met	Ala	Ala		Pro
			260					265					270	-	
Leu	Leu	Val	Pro	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Gln	Tyr
		275					280					285			
Gly	Glu	Asp	Met	Gly	His	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr	Glu
	290					295					300				
Arg	Val	Leu	Gln	Gly	Leu	Leu	Gly	Pro	Ile	Phe	Lys	Asn	Thr	Ser	Val
305					310					315					320
Gly	Pro	Leu	Tyr		Gly	Cys	Arg	Leu		Ser	Leu	Arg	Ser		Lys
_		_ •		325			_		330	_			•	335	_
Asp	GTA	Ата		Thr	GTĀ	Val	Asp		ITe	Суѕ	lle	His		Leu	Asp
Desa	*	C	340	C1	<b>T</b>	n	*****	345	N	T	M	m	350	*	0
Pro	газ		Pro	CTA	ьeи	Asn		GLU	Arg	ren	Tyr	Trp	GLU	ьеп	ser
Gln	Ť ou	355	7 co	61.0	т1.	Tuo	360	Tour	C1++	Dro	Tree.	365 Thr	Ton	7 on	7~~
GIII	370	1111	POII	GTA	TTE	375	GIU	neu	сту	FIO	380	TIIT	пеп	Asp	ALG
Asn		Len	Tvr	Val	Asn		Ala	Glv	Pro	Len		Val	Len	Phe	Thr
385	-		-3-		390			O.L.y		395		V 04.12	204		400
	_														
ьeu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Lys	Tyr	Glu	Glu	Asp	Met	His	Arq
ьeu	Asn	Phe	Thr	Ile 405	Thr	Asn	Leu	Lys	Tyr 410	Glu	Glu	Asp	Met	His 415	Arg
				405				_	410			-		415	_
Pro	Gly	Ser	Arg 420	405 Lys	Phe	Asn	Thr	Thr 425	410 Glu	Arg	Val	Leu	Gln 430	415 Thr	Leu
Pro	Gly	Ser	Arg 420	405 Lys	Phe	Asn	Thr Thr	Thr 425	410 Glu	Arg	Val	Leu Leu	Gln 430	415 Thr	Leu
Pro Arg	Gly Gly	Ser Pro 435	Arg 420 Met	405 Lys Phe	Phe Lys	Asn Asn	Thr Thr 440	Thr 425 Ser	410 Glu Gly	Arg Gly	Val Leu	Leu Leu 445	Gln 430 Tyr	415 Thr Ser	Leu Gly
Pro Arg	Gly Gly Arg	Ser Pro 435	Arg 420 Met	405 Lys Phe	Phe Lys	Asn Asn Arg	Thr Thr 440	Thr 425 Ser	410 Glu Gly	Arg Gly	Val Leu Gly	Leu Leu	Gln 430 Tyr	415 Thr Ser	Leu Gly
Pro Arg Cys	Gly Gly Arg 450	Ser Pro 435 Leu	Arg 420 Met Thr	405 Lys Phe Leu	Phe Lys Leu	Asn Asn Arg 455	Thr Thr 440 Ser	Thr 425 Ser Glu	410 Glu Gly Lys	Arg Gly Asp	Val Leu Gly 460	Leu Leu 445 Ala	Gln 430 Tyr Ala	415 Thr Ser Thr	Leu Gly Gly
Pro Arg Cys Val	Gly Gly Arg 450	Ser Pro 435 Leu	Arg 420 Met Thr	405 Lys Phe Leu	Phe Lys Leu Thr	Asn Asn Arg 455	Thr Thr 440 Ser	Thr 425 Ser Glu	410 Glu Gly Lys Asp	Arg Gly Asp Pro	Val Leu Gly 460	Leu Leu 445	Gln 430 Tyr Ala	415 Thr Ser Thr	Leu Gly Gly Val
Pro Arg Cys Val 465	Gly Gly Arg 450 Asp	Ser Pro 435 Leu Ala	Arg 420 Met Thr	405 Lys Phe Leu Cys	Phe Lys Leu Thr 470	Asn Asn Arg 455 His	Thr Thr 440 Ser Arg	Thr 425 Ser Glu Leu	410 Glu Gly Lys Asp	Arg Gly Asp Pro 475	Val Leu Gly 460 Lys	Leu Leu 445 Ala Ser	Gln 430 Tyr Ala Pro	415 Thr Ser Thr Gly	Leu Gly Gly Val 480
Pro Arg Cys Val 465	Gly Gly Arg 450 Asp	Ser Pro 435 Leu Ala	Arg 420 Met Thr	405 Lys Phe Leu Cys Leu	Phe Lys Leu Thr 470	Asn Asn Arg 455 His	Thr Thr 440 Ser Arg	Thr 425 Ser Glu Leu	410 Glu Gly Lys Asp Ser	Arg Gly Asp Pro 475	Val Leu Gly 460 Lys	Leu Leu 445 Ala	Gln 430 Tyr Ala Pro	415 Thr Ser Thr Gly	Leu Gly Gly Val 480
Pro Arg Cys Val 465 Asp	Gly Gly Arg 450 Asp	Ser Pro 435 Leu Ala Glu	Arg 420 Met Thr Ile Gln	405 Lys Phe Leu Cys Leu 485	Phe Lys Leu Thr 470 Tyr	Asn Asn Arg 455 His	Thr Thr 440 Ser Arg	Thr 425 Ser Glu Leu	410 Glu Gly Lys Asp Ser 490	Arg Gly Asp Pro 475 Gln	Val Leu Gly 460 Lys Leu	Leu Leu 445 Ala Ser	Gln 430 Tyr Ala Pro Asn	415 Thr Ser Thr Gly Gly 495	Leu Gly Gly Val 480 Ile
Pro Arg Cys Val 465 Asp	Gly Gly Arg 450 Asp	Ser Pro 435 Leu Ala Glu	Arg 420 Met Thr Ile Gln Gly	405 Lys Phe Leu Cys Leu 485 Pro	Phe Lys Leu Thr 470 Tyr	Asn Asn Arg 455 His Trp	Thr 440 Ser Arg Glu Leu	Thr 425 Ser Glu Leu Leu	410 Glu Gly Lys Asp Ser 490 Arg	Arg Gly Asp Pro 475 Gln Asn	Val Leu Gly 460 Lys Leu Ser	Leu Leu 445 Ala Ser Thr	Gln 430 Tyr Ala Pro Asn	415 Thr Ser Thr Gly 495 Val	Leu Gly Gly Val 480 Ile
Pro Arg Cys Val 465 Asp Lys	Gly Arg 450 Asp Arg	Ser Pro 435 Leu Ala Glu Leu	Arg 420 Met Thr Ile Gln Gly 500	405 Lys Phe Leu Cys Leu 485 Pro	Phe Lys Leu Thr 470 Tyr	Asn Arg 455 His Trp	Thr 440 Ser Arg Glu Leu	Thr 425 Ser Glu Leu Leu Asp 505	410 Glu Gly Lys Asp Ser 490 Arg	Arg Gly Asp Pro 475 Gln Asn	Val Leu Gly 460 Lys Leu Ser	Leu 445 Ala Ser Thr	Gln 430 Tyr Ala Pro Asn Tyr 510	415 Thr Ser Thr Gly Gly 495 Val	Leu Gly Gly Val 480 Ile Asn
Pro Arg Cys Val 465 Asp Lys	Gly Arg 450 Asp Arg	Ser Pro 435 Leu Ala Glu Leu	Arg 420 Met Thr Ile Gln Gly 500	405 Lys Phe Leu Cys Leu 485 Pro	Phe Lys Leu Thr 470 Tyr	Asn Arg 455 His Trp	Thr 440 Ser Arg Glu Leu	Thr 425 Ser Glu Leu Leu Asp 505	410 Glu Gly Lys Asp Ser 490 Arg	Arg Gly Asp Pro 475 Gln Asn	Val Leu Gly 460 Lys Leu Ser	Leu Leu 445 Ala Ser Thr	Gln 430 Tyr Ala Pro Asn Tyr 510	415 Thr Ser Thr Gly Gly 495 Val	Leu Gly Gly Val 480 Ile Asn
Pro Arg Cys Val 465 Asp Lys Gly	Gly Gly Arg 450 Asp Arg Glu Phe	Ser Pro 435 Leu Ala Glu Leu Thr 515	Arg 420 Met Thr Ile Gln Gly 500 His	405 Lys Phe Leu Cys Leu 485 Pro	Phe Lys Leu Thr 470 Tyr Tyr	Asn Asn Arg 455 His Trp Thr	Thr 440 Ser Arg Glu Leu Val 520	Thr 425 Ser Glu Leu Leu Asp 505 Pro	410 Glu Gly Lys Asp Ser 490 Arg	Arg Gly Asp Pro 475 Gln Asn Xaa	Val Leu Gly 460 Lys Leu Ser	Leu 445 Ala Ser Thr Leu Thr 525	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro	415 Thr Ser Thr Gly 495 Val	Leu Gly Gly Val 480 Ile Asn
Pro Arg Cys Val 465 Asp Lys Gly	Gly Gly Arg 450 Asp Arg Glu Phe	Ser Pro 435 Leu Ala Glu Leu Thr 515	Arg 420 Met Thr Ile Gln Gly 500 His	405 Lys Phe Leu Cys Leu 485 Pro	Phe Lys Leu Thr 470 Tyr Tyr	Asn Asn Arg 455 His Trp Thr	Thr 440 Ser Arg Glu Leu Val 520	Thr 425 Ser Glu Leu Leu Asp 505 Pro	410 Glu Gly Lys Asp Ser 490 Arg	Arg Gly Asp Pro 475 Gln Asn Xaa	Val Leu Gly 460 Lys Leu Ser	Leu 445 Ala Ser Thr Leu Thr	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro	415 Thr Ser Thr Gly 495 Val	Leu Gly Gly Val 480 Ile Asn
Pro Arg Cys Val 465 Asp Lys Gly Ser	Gly Gly Arg 450 Asp Arg Glu Phe Thr 530	Pro 435 Leu Ala Glu Leu Thr 515 Val	Arg 420 Met Thr Ile Gln Gly 500 His	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu	Phe Lys Leu Thr 470 Tyr Tyr Thr	Asn Arg 455 His Trp Thr Ser Thr 535	Thr 440 Ser Arg Glu Leu Val 520 Ser	Thr 425 Ser Glu Leu Leu Asp 505 Pro	410 Glu Gly Lys Asp Ser 490 Arg	Arg Gly Asp Pro 475 Gln Asn Xaa Pro	Val Leu Gly 460 Lys Leu Ser Ser Phe 540	Leu 445 Ala Ser Thr Leu Thr 525	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro	415 Thr Ser Thr Gly 495 Val Gly Pro	Leu Gly Gly Val 480 Ile Asn Thr
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val	Arg 420 Met Thr Ile Gln Gly 500 His Asp	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550	Asn Asn Arg 455 His Trp Thr Ser Thr 535 Leu	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val	410 Glu Gly Lys Asp Ser 490 Arg Thr	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr	Leu Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn	415 Thr Ser Thr Gly 495 Val Gly Pro	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val	Arg 420 Met Thr Ile Gln Gly 500 His Asp	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550	Asn Asn Arg 455 His Trp Thr Ser Thr 535 Leu	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr	Leu Leu 445 Ala Ser Thr Leu Thr 525 Ser	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn	415 Thr Ser Thr Gly 495 Val Gly Pro	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn	Arg 420 Met Thr Ile Gln 500 His Asp Ala Leu	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550 Tyr	Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr	Leu Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu Pro	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn	Arg 420 Met Thr Ile Gln Gly 500 His Asp Ala Leu Thr	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550 Tyr	Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val Asp Leu	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr	Leu Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile Lys	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala Thr	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn Asn	Arg 420 Met Thr Ile Gln Gly 500 His Asp Ala Leu Thr 580	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565 Thr	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550 Tyr	Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu Arg	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu Val	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val Asp Leu 585	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570 Gln	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr Arg	Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu Pro	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly Gly 590	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575 Pro	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile Lys	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala Thr	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn Asn	Arg 420 Met Thr Ile Gln Gly 500 His Asp Ala Leu Thr 580	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565 Thr	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550 Tyr	Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu Arg	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu Val Leu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val Asp Leu 585	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570 Gln	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr Arg	Leu Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu Pro Leu Cys	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly Gly 590	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575 Pro	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile Lys Phe	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala Thr Phe Lys	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn Asn 595	Arg 420 Met Thr Ile Gln Gly 500 His Asp Ala Leu Thr 580 Thr	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565 Thr	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550 Tyr Glu Val	Asn Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu Arg Gly	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu Val Leu Olu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val Asp Leu 585 Leu	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570 Gln Tyr	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His Thr	Val Leu Gly 460 Lys Leu Ser Ser Phe 540 Thr Arg Leu Gly	Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu Pro Leu Cys 605	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly Gly 590 Arg	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575 Pro Leu	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg Met Thr
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile Lys Phe	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala Thr Phe Lys Leu	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn Asn 595	Arg 420 Met Thr Ile Gln Gly 500 His Asp Ala Leu Thr 580 Thr	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565 Thr	Phe Lys Leu Thr 470 Tyr Tyr Thr Gly Pro 550 Tyr Glu Val	Asn Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu Arg Gly Asp	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu Val Leu Olu	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val Asp Leu 585 Leu	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570 Gln Tyr	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His Thr	Val Leu Gly 460 Lys Leu Ser Phe 540 Thr Arg Leu Gly	Leu Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu Pro Leu Cys	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly Gly 590 Arg	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575 Pro Leu	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg Met Thr
Pro Arg Cys Val 465 Asp Lys Gly Ser Pro 545 Ile Lys Phe Leu	Gly Gly Arg 450 Asp Glu Phe Thr 530 Ala Thr Phe Lys Leu 610	Ser Pro 435 Leu Ala Glu Leu Thr 515 Val Thr Asn Asn 595 Arg	Arg 420 Met Thr Ile Gln Gly 500 His Asp Ala Leu Thr 580 Thr Ser	405 Lys Phe Leu Cys Leu 485 Pro Arg Leu Gly Lys 565 Thr Ser Glu	Phe Lys Leu Thr 470 Tyr Thr Gly Pro 550 Tyr Glu Val Lys	Asn Asn Arg 455 His Trp Thr Ser Thr 535 Leu Glu Arg Gly Asp 615	Thr 440 Ser Arg Glu Leu Val 520 Ser Leu Glu Val Leu 600 Gly	Thr 425 Ser Glu Leu Leu Asp 505 Pro Gly Val Asp Leu 585 Leu	410 Glu Gly Lys Asp Ser 490 Arg Thr Thr Leu Met 570 Gln Tyr Xaa	Arg Gly Asp Pro 475 Gln Asn Xaa Pro Phe 555 His Thr Ser Thr	Val Leu Gly 460 Lys Leu Ser Phe 540 Thr Arg Leu Gly 620	Leu 445 Ala Ser Thr Leu Thr 525 Ser Leu Pro Leu Cys 605	Gln 430 Tyr Ala Pro Asn Tyr 510 Pro Leu Asn Gly 590 Arg	415 Thr Ser Thr Gly 495 Val Gly Pro Phe Ser 575 Pro Leu	Leu Gly Gly Val 480 Ile Asn Thr Ser Thr 560 Arg Met Thr

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COE					C20					COE					C40
625	ጥላታ	Trn	Glu	Ton	630	Gln	7.011	Ψh.~	7 en	635	Tla	T.ve	61	Lou	640
				645					650	-				655	-
Pro	Tyr	Thr	Leu 660	Asp	Arg	Xaa	Ser	Leu 665	Tyr	Val	Asn	Gly	Phe 670	Thr	His
Trp	Ile	Pro 675	Val	Pro	Thr	Ser	Ser 680	Thr	Pro	Gly	Thr	Ser 685	Thr	Val	Asp
Leu	Gly 690		Gly	Thr	Pro	Ser 695		Leu	Pro	Ser	Pro		Thr	Ala	Gly
Pro 705	Leu	Leu	Val	Pro	Phe 710	Thr	Leu	Asn	Phe	Thr 715	Ile	Thr	Asn	Leu	Gln 720
Tyr	Glu	Glu	Asp	Met 725	His	His	Pro	Gly	Ser 730	Arg	гля	Phe	Asn	Thr 735	Thr
Glu	Arg	Val	Leu 740	Gln	Gly	Leu	Leu	Gly 745		Met	Phe	Lys	Asn 750	_	Ser
Val	Gly	Leu 755	Leu	Tyr	Ser	Gly	Cys 760	Arg	Leu	Thr	Leu	Leu 765	Arg	Pro	Glu
Lys	Asn 770	Gly	Ala	Ala	Thr	Gly 775	Met	Asp	Ala	Ile	Cys 780	Ser	His	Arg	Leu
Asp 785	Pro	Lys	Ser	Pro	Gly 790	Leu	Asn	Arg	Glu	Gln 795	Leu	Tyr	Trp	Glu	Leu 800
Ser	Gln	Leu	Thr	His 805	Gly	Ile	Lys	Glu	Leu 810	Gly	Pro	Tyr	Thr	Leu 815	Asp
Arg	His	Ser	Leu 820	Tyr	Val	Asn	Gly	Phe 825	Thr	His	Trp	Ile	Pro 830	Val	Pro
Thr	Ser	Ser 835	Thr	Pro	Gly	Thr	Ser 840	Thr	Val	Asp	Leu	Gly 845	Ser	Gly	Thr
	850					Pro 855				-	860				
Phe 865	Thr	Leu	Asn	Phe	Thr 870	Ile	Thr	Asn	Leu	Xaa 875	Tyr	Glu	Glu	Asp	Met 880
				885		Lys			890					895	
Ser	Leu	Leu	Gly 900	Pro	Met	Phe	Lys	Asn 905	Thr	Ser	Val	Gly	Pro 910	Leu	Tyr
		915				Leu	920	_			-	925			
Thr	Gly 930	Val	Asp	Ala	Ile	Cys 935	Thr	His	Arg	Leu	Asp 940	Pro	Lys	Ser	Pro
Gly 945	Val	Asp	Arg	Glu	Gln 950	Leu	Tyr	Trp	Glu	Leu 955	Ser	G1n	Leu	Thr	Asn 960
		_		965	_	Pro	_		970	_				975	_
		_	980			Gln		985					990		
Gly	Thr	Ser 995	Thr	Val	Asp	Leu ·	Gly 1000		Ser	Gly	Thr	Pro 1009	_	Ser	Leu
	1010	)				Gly 1015	5				1020	)			
Phe 1025		Ile	Thr	Asn	Leu 1030	Gln )	Tyr	Glu	Glu	Asp 1035		His	His	Pro	Gly 1040
Ser	Arg	Lys	Phe	Asn 1045		Thr	Glu	Arg	Val 1050		Gln	Gly	Leu	Leu 105	
Pro	Met	Phe	Lys 1060		Thr	Ser	Val	Glŷ 1065		Leu	Tyr	Ser	Gly 1070		Arg
Leu	Thr	Leu 1075		Arg	Pro	Glu	Lys 1080		Gly	Ala	Ala	Thr 1085		Met	Asp
Ala	Ile	Cys	Ser	His	Arg	Leu	Asp	Pro	Lys	Ser	Pro	Gly	Leu	Asn	Arg

1090	109	5	110	0	
Glu Gln Leu Tyr 1105	Trp Glu Leu 1110	Ser Gln L	eu Thr His	Gly Ile	Lys Glu 1120
Leu Gly Pro Tyr	Thr Leu Asp 1125		er Leu Tyr 130	Val Asn	Gly Phe 1135
Thr His Arg Ser 1140		Pro Thr S 1145	er Thr Pro	Gly Thr	
Val Asp Leu Gly 1155	Thr Ser Gly	Thr Pro S 1160	er Ser Leu	Pro Ser 1165	Pro Thr
Thr Ala Val Pro 1170	Leu Leu Val 117		hr Leu Asr 118		Ile Thr
Asn Leu Gln Tyr 1185	1190	_	1195	_	1200
	1205	1	210		1215
Asn Ser Ser Val 1220	)	1225		123	0
Arg Ser Glu Lys 1235		1240		1245	
His His Leu Asn 1250	125	5	126	0	
Trp Gln Leu Ser 1265	1270		1275		1280
	1285	. 1	290		1295
Ser Gly Leu Thr	j	1305		131	0 -
Thr Ser Gly Thr 1315		1320		1325	
Leu Leu Val Pro 1330	133	5	134	0	
Glu Glu Asp Met 1345	1350		1355		1360
	1365	1	370		1375
Gly Pro Leu Tyr 1380	1	1385		139	0
Asp Gly Ala Ala 1395		1400		1405	
Pro Lys Arg Pro 1410	141	5	142	0	
Gln Leu Thr His 1425	1430		1435		1440
	1445	1	450		1455
Thr Ser Thr Pro 1460	)	1465		147	0
Pro Ser Ser Phe 1475		1480		1485	
Phe Thr Phe Asn 1490	149	5	150	0 '	
Gln His Pro Gly 1505	1510		1515	_	1520
Gly Leu Leu Thr	Pro Leu Phe 1525		hr Ser Val 530	Gly Pro	Leu Tyr 1535
Ser Gly Cys Arg 1540	Leu Thr Leu			Gln Glu 155	Ala Ala
Thr Gly Xaa Asp	Thr Ile Cys		rg Xaa Asp		

1555 1560 . Gly Leu Asp Arg Glu Xaa Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Xaa Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr 1590 1595 1600 Val Asn Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr Pro 1605 1610 1615 Gly Thr Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser Leu 1620 1625 1630 Pro Gly His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu Asn 1645. 1635 1640 Phe Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly 1650 1655 1660 Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys 1665 1670 1675 Pro Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 1685 1690 1695 Leu Thr Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val Asp 1700 1705 1710 Ala Ile Cys Thr Leu Arg Leu Asp Pro Thr Gly Pro Gly Leu Asp Arg 1715 1720 1725 Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Ser Val Thr Glu 1730 1735 1740 Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe 1745 1750 1755 Thr His Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Ser Ala 1765 1770 1775 Val His Leu Glu Thr Ser Gly Thr Pro Ala Ser Leu Pro Gly His Thr 1780 1785 1790 Ala Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr 1795 1800 1805 Asn Leu Gln Tyr Glu Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe 1810 · 1815 1820 Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys 1835 1830 Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 1845 1850 Arg Pro Glu Lys Arg Gly Ala Ala Thr Gly Val Asp Thr Ile Cys Thr 1865 His Arg Leu Asp Pro Leu Asn Pro Gly Leu Asp Arg Glu Gln Leu Tyr 1875 1880 1885 Trp Glu Leu Ser Lys Leu Thr Cys Gly Ile Ile Glu Leu Gly Pro Tyr 1895 Leu Leu Asp Arg Gly Ser Leu Tyr Val Asn Gly Phe Thr His Arg Asn 1905 1910 1915 Phe Val Pro Ile Thr Ser Thr Pro Gly Thr Ser Thr Val His Leu Gly 1925 1930 Thr Ser Glu Thr Pro Ser Ser Leu Pro Arg Pro Ile Val Pro Gly Pro 1940 1945 1950 Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr 1960 1955 Glu Glu Ala Met Arg His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu 1975 1980 Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Ile 1985 1990 1995 Gly Pro Leu Tyr Ser Ser Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys 2005 2010 2015 Asp Lys Ala Ala Thr Arg Val Asp Ala Ile Cys Thr His His Pro Asp

			2020	)				2025	5				2030	)	
Pro	Gln	Ser 2035	Pro		Leu	Asn	Arg 2040	Glu		Leu	Tyr	Trp 2045	Glu	Leu	Ser
Gln	Leu 2050		His	Gly	Ile	Thr 2055		Leu	Gly	Pro	Tyr 2060		Leu	Asp	Arg
Xaa 206	Ser		Tyr	Val	Xaa 2070	Gly		Thr	His	Trp 2075		Pro	Ile	Pro	Thr 2080
		Thr	Pro	Gly 2085		Ser	Ile		Asn 2090		Gly	Thr	Ser	Gly 2095	
Pro	Pro	Ser	Leu 2100		Glu	Thr	Thr	Ala 2105		Gly	Pro	Leu	Leu 2110	Val	Pro
Phe	Thr	Leu 2115		Phe	Thr	Ile	Thr 2120		Leu	Gln	Tyr	Glu 2125		Asn	Met
Gly	His 2130		Gly	Ser	Arg	Lys 2135		Asn	Ile	Thr	Glu 2140		Val	Leu	Gln
Gly 2145		Leu	Ьys	Pro	Leu 2150		Lys	Ser	Thr	Ser 2155		Gly	Pro	Leu	Tyr 2160
	_	_	_	2165	5			_	2170	)	_			Val 2175	<b>,</b>
			2180	)				2185	5				2190		
		2195	5				2200	)				2205	5	Thr	
Ser	Ile 2210		Glu	Leu	Gly	Pro 2215	-	Thr	Leu	Asp	Arg 2220		Ser	Leu	Tyr
Val 2225		Gly	Phe	Thr	Gln 2230		Ser	Ser	Val	Pro 2235		Thr	Ser	Thr	Pro 2240
Gly	Thr	Phe	Thr	Val 2245		Pro	Glu	Thr	Ser 2250		Thr	Pro	Ser	Ser 2255	
Pro	Gly	Pro	Thr 2260		Thr	Gly	Pro	Val 2265		Leu	Pro	Phe	Thr 2270	Leu )	Asn
Phe	Thr	Tle	TIO	Zen	TON	~1 ~	M	C1	~~~	*	M-+	Uic	7	Dec	C1
		2275	5				2280	)		_		2285	5		_
	Arg 2290	2275 Lys )	) Phe	Asn	Thr	Thr 2295	2280 Glu 5	) Arg	Val	Leu	Gln 2300	2285 Gly )	Leu	Leu	Met
Pro 2305	Arg 229( Leu	2275 Lys ) Phe	Phe Lys	Asn Asn	Thr Thr 2310	Thr 2295 Ser	228( Glu 5 Val	Arg Ser	Val Ser	Leu Leu 2315	Gln 2300 Tyr	2285 Gly ) Ser	Leu Gly	Leu Cys	Met Arg 2320
Pro 2305 Leu	Arg 229( Leu Thr	2275 Lys ) Phe Leu	Phe Lys Leu	Asn Asn Arg 2325	Thr Thr 2310 Pro	Thr 2295 Ser ) Glu	228( Glu 5 Val Lys	Arg Ser Asp	Val Ser Gly 2330	Leu Leu 2315 Ala	Gln 2300 Tyr Ala	2285 Gly ) Ser Thr	Leu Gly Arg	Leu Cys Val 2335	Met Arg 2320 Asp
Pro 2305 Leu Ala	Arg 2290 Leu Thr Val	2275 Lys ) Phe Leu Cys	Phe Lys Leu Thr 2340	Asn Asn Arg 2325 His	Thr Thr 2310 Pro Arg	Thr 2295 Ser ) Glu Pro	2280 Glu Val Lys Asp	Arg Ser Asp Pro 234	Val Ser Gly 2330 Lys	Leu Leu 2315 Ala ) Ser	Gln 2300 Tyr Ala Pro	2285 Gly ) Ser Thr	Leu Gly Arg Leu 2350	Leu Cys Val 2335 Asp	Met Arg 2320 Asp Arg
Pro 2305 Leu Ala Glu	Arg 2290 Leu Thr Val	Leu Cys Leu 2355	Phe Lys Leu Thr 2340 Tyr	Asn Arg 2325 His ) Trp	Thr Thr 2310 Pro Arg	Thr 2295 Ser Glu Pro	2280 Glu Val Lys Asp Ser 2360	Arg Ser Asp Pro 2345 Gln	Val Ser Gly 2330 Lys Leu	Leu 2315 Ala Ser Thr	Gln 2300 Tyr Ala Pro	Gly Ser Thr Gly Gly 2365	Leu Gly Arg Leu 2350	Leu Cys Val 2335 Asp ) Thr	Met Arg 2320 Asp Arg Glu
Pro 2305 Leu Ala Glu Leu	Arg 2290 Leu Thr Val Arg Gly 2370	Leu Cys Leu 2355 Pro	Phe Lys Leu Thr 2340 Tyr	Asn Arg 2325 His Trp	Thr 2310 Pro Arg Lys	Thr 2295 Ser Glu Pro Leu Asp 2375	2280 Glu Val Lys Asp Ser 2360 Arg	Arg Ser Asp Pro 2345 Gln His	Val Ser Gly 2330 Lys Leu Ser	Leu 2315 Ala Ser Thr	Gln 2300 Tyr Ala Pro His Tyr 2380	2285 Gly Ser Thr Gly 2365 Val	Leu Gly Arg Leu 2350 Ile Asn	Leu Cys Val 2335 Asp ) Thr	Met Arg 2320 Asp Arg Glu Phe
Pro 2305 Leu Ala Glu Leu	Arg 2290 Leu 5 Thr Val Arg Gly 2370 His	Leu Cys Leu 2355 Pro	Phe Lys Leu Thr 2340 Tyr	Asn Arg 2325 His Trp	Thr 2310 Pro Arg Lys	Thr 2295 Ser Glu Pro Leu Asp 2375	2280 Glu Val Lys Asp Ser 2360 Arg	Arg Ser Asp Pro 2345 Gln His	Val Ser Gly 2330 Lys Leu Ser	Leu 2315 Ala Ser Thr	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro	2285 Gly Ser Thr Gly 2365 Val	Leu Gly Arg Leu 2350 Ile Asn	Leu Cys Val 2335 Asp ) Thr	Met Arg 2320 Asp Arg Glu Phe
Pro 2305 Leu Ala Glu Leu Thr 2385	Arg 2290 Leu Thr Val Arg Gly 2370 His	2275 Lys ) Phe Leu Cys Leu 2355 Pro ) Gln	Phe Lys Leu Thr 2340 Tyr Ser	Asn Arg 2325 His Trp Thr	Thr 2310 Pro Arg Lys Leu Met 2390 Ser	Thr 2295 Ser Glu Pro Leu Asp 2375 Thr	2280 Glu Val Lys Asp Ser 2360 Arg	Arg Ser Asp Pro 2345 Gln His	Val Ser Gly 2330 Lys Leu Ser	Leu Leu 2315 Ala Ser Thr Leu Thr 2395 Ser	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro	2285 Gly Ser Thr Gly 2365 Val	Leu Gly Arg Leu 2350 Ile Asn	Leu Cys Val 2335 Asp ) Thr	Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr
Pro 2305 Leu Ala Glu Leu Thr 2385 Met	Arg 2290 Leu Thr Val Arg Gly 2370 His	Leu Leu Los Pro Cys Leu Los Pro Leu Leu	Phe Lys Leu Thr 234( Tyr Tyr Ser Ala	Asn Arg 2325 His Trp Thr Ser Thr 2405 Leu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser	Thr 2295 Ser Glu Pro Leu Asp 2375 Thr	2280 Glu Val Lys Asp Ser 2360 Arg Thr	Arg Ser Asp Pro 2345 Gln His Thr	Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410	Leu Leu 2315 Ala Ser Thr Leu Thr 2395 Ser	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro	2285 Gly Ser Thr Gly 2365 Val Asp	Leu Gly Arg Leu 2350 Ile Asn Thr	Leu Cys Val 2335 Asp Thr Gly Ser Pro 2415 Ile	Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr
Pro 2305 Leu Ala Glu Leu Thr 2385 Met Thr Asn	Arg 2290 Leu Thr Val Arg Gly 2370 His His Leu	Leu Cys Leu 2355 Pro Gln Leu Ser Arg	Phe Lys Leu Thr 234( Tyr Tyr Ser Ala Pro 242( Tyr	Asn Arg 2325 His Trp Thr Ser Thr 2405 Leu Glu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser Leu Glu	Thr 2295 Ser Glu Pro Leu Asp 2375 Thr Arg Val	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr Leu Met 2440	Arg Ser Asp Pro 2345 Gln His Thr Pro Phe 2425 His	Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr	Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro Leu Asn	2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445	Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg	Leu Cys Val 2335 Asp Thr Gly Ser Pro 2415 Ile Lys	Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr
Pro 2305 Leu Ala Glu Leu Thr 2385 Met Thr Asn	Arg 2290 Leu Thr Val Arg Gly 2370 His His Leu	Leu Cys Leu 2355 Pro Gln Leu Ser Arg 2435 Thr	Phe Lys Leu Thr 234( Tyr Tyr Ser Ala Pro 242( Tyr	Asn Arg 2325 His Trp Thr Ser Thr 2405 Leu Glu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser Leu Glu	Thr 2295 Ser Glu Pro Leu Asp 2375 Thr Arg Val	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr Leu Met 2440 Gln	Arg Ser Asp Pro 2345 Gln His Thr Pro Phe 2425 His	Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr	Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro Leu Asn	2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445 Pro	Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg	Leu Cys Val 2335 Asp Thr Gly Ser Pro 2415 Ile	Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr
Pro 2305 Leu Ala Glu Leu Thr 2385 Met Thr Asn Asn 2465	Arg 2290 Leu Thr Val Arg Gly 2370 His His Leu Thr 2450	Leu Cys Leu 2355 Pro Gln Leu Ser Arg 2435 Thr	Phe Lys Leu Thr 234( Tyr Tyr Ser Ala Pro 242( Tyr Glu Val	Asn Arg 2325 His Trp Thr Ser Z405 Leu Glu Arg Gly	Thr 2310 Pro Arg Lys Leu Met 2390 Ser Cleu Glu Val Pro 2470	Thr 2295 Ser Glu Pro Leu Asp 2375 Thr Val Asn Leu 2455 Leu	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr Leu Met 2440 Gln	Arg Ser Asp Pro 2345 Gln His Thr Pro Phe 2425 His Gly Ser	Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr His Leu	Leu Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile Pro Leu Cys 2475	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro Leu Asn Gly Arg 2460 Arg	2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445 Pro Leu	Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg Val	Leu Cys Val 2335 Asp Thr Gly Ser Pro 2415 Ile Lys	Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr Lys Leu 2480

	2485	24	90 -	2495
Tyr Arg Pro Asp 250	_	Pro Gly Le 2505	u Asp Arg Glu	Gln Leu Tyr 2510
Trp Glu Leu Ser 2515	Gln Leu Thr	His Ser Il 2520	e Thr Glu Leu 252	
Thr Leu Asp Arg 2530	253	5	2540	_
Ser Val Pro Thr 2545	Thr Ser Ile 2550	Pro Gly Th	r Pro Thr Val 2555	Asp Leu Gly 2560
Thr Ser Gly Thr	Pro Val Ser 2565		y Pro Ser Ala 70 .	Ala Ser Pro 2575
Leu Leu Val Leu 258		Asn Phe Th 2585	r Ile Thr Asn	Leu Arg Tyr 2590
Glu Glu Asn Met 2595	Gln His Pro	Gly Ser Ar 2600	g Lys Phe Asn 260	
Arg Val Leu Gln 2610	261	5	2620	
Gly Pro Leu Tyr 2625	2630	•	2635	2640
Asp Gly Thr Ala	2645	26	50	2655
Pro Lys Ser Pro 266	0	2665		2670
Gln Leu Thr His 2675		2680	268	5
Asp Ser Leu Phe 2690	269	5	2700	
Thr Ser Thr Pro 2705	2710		2715	2720
Pro Ala Ser Ile	2725	27	30	2735
Phe Thr Leu Asn 274	0	2745		2750
Trp Pro Gly Ser 2755		2760	276	5
Leu Leu Arg Pro 2770	277.	5	2780	
Gly Cys Arg Leu 2785	2790		2795	2800
Gly Val Asp Ala	2805	28	10	2815
Leu Asp Arg Glu 282	0	2825		2830
Ile Thr Glu Leu 2835		2840	284	5
Asn Gly Phe Thr 2850	285	5	2860	
Val Ser Glu Glu 2865	Pro Phe Thr 2870	Leu Asn Ph	e Thr Ile Asn 2875	Asn Leu Arg 2880
Tyr Met Ala Asp	Met Gly Gln 2885		r Leu Lys Phe 90	Asn Ile Thr 2895
Asp Asn Val Met 290	0	2905		2910
Leu Gly Ala Arg 2915	Tyr Thr Gly	Cys Arg Va 2920	l Ile Ala Leu 292	_
Lys Asn Gly Ala 2930	Glu Thr Arg 293		u Leu Cys Thr 2940	Tyr Leu Gln

2945	2950		2955		2960
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Lys Asp Ser Leu 298	_	sn Gly Tyr 2985		Gly Xaa 2990	
Pro Pro Thr Thr 2995	Pro Lys Pr	ro Ala Thr 3000	Thr Phe Let	Pro Pro 3005	Leu Ser
Glu Ala Thr Thr 3010		ly Tyr His 015	Leu Lys Th		Leu Asn
Phe Thr Ile Ser 3025	Asn Leu Gl 3030	ln Tyr Ser	Pro Asp Met 3035	: Gly Lys	Gly Ser 3040
Ala Thr Phe Asn	3045	_	3050		3055
Leu Phe Gln Lys 306	)	3065	5	307	0
Ile Ser Leu Arg 3075		3080		3085	
Thr Cys Thr Tyr 3090	30	095	31	00	
Gln Leu Tyr Trp 3105	3110		3115		3120
Gly Phe Tyr Val	3125		3130		3135
Pro Gln Asn Leu 314	)	3145	5	315	0
Val Asn Trp Asn 3155		3160		3165	
Thr Leu Leu Arg 3170	_	ln Asp Lys 175	Val Thr Th:		ras GTA
Ser Gln Leu His 3185	3190		3195		3200
Met Asp Ser Val	Leu Val Th	nr Val Lys	Ala Leu Pho 3210	e Ser Ser	Asn Leu 3215
Asp Pro Ser Leu 322	)	3225	5	323	0
322 Ser Phe His Trp 3235	) Leu Gly Se	3225 er Thr Tyr 3240	Gln Leu Va	323 L Asp Ile 3245	0 His Val
322 Ser Phe His Trp 3235 Thr Glu Met Glu 3250	Leu Gly Se Ser Ser Va 32	3225 er Thr Tyr 3240 al Tyr Gln 255	Gln Leu Va Pro Thr Se 32	3230 Asp Ile 3245 r Ser Ser 50	O His Val Ser Thr
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Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270	3225 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile	Gln Leu Va Pro Thr Se 32 Thr Asn Le 3275	3230 Asp Ile 3245 r Ser Ser 60 1 Pro Tyr	O His Val Ser Thr Ser Gln 3280
322 Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr 3265	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270 Pro Gly Th 3285 Leu Asn Gl	3225 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile hr Thr Asn	Gln Leu Va Pro Thr Se 32 Thr Asn Le 3275 Tyr Gln Ar 3290 Arg Asn Se	3230 Asp Ile 3245 r Ser Ser 50 1 Pro Tyr g Asn Lys	Mis Val Ser Thr Ser Gln 3280 Arg Asn 3295 Lys Ser
322 Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr 3265 Asp Lys Ala Gln Ile Glu Asp Ala	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270 Pro Gly Th 3285 Leu Asn Gl	3225 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile hr Thr Asn ln Leu Phe 3305	Gln Leu Va Gln Leu Va Pro Thr Se 32 Thr Asn Le 3275 Tyr Gln Ar 3290 Arg Asn Se	3230 1 Asp Ile 3245 r Ser Ser 50 1 Pro Tyr g Asn Lys r Ser Ile 331	Mis Val Ser Thr Ser Gln 3280 Arg Asn 3295 Lys Ser
Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr 3265 Asp Lys Ala Gln Ile Glu Asp Ala 330 Tyr Phe Ser Asp	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270 Pro Gly Th 3285 Leu Asn Gl Cys Gln Va	3225 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile hr Thr Asn ln Leu Phe 3305 al Ser Thr 3320	Gln Leu Value Pro Thr Se 32 Thr Asn Le 3275 Tyr Gln Ar 3290 Arg Asn Se 50 Phe Arg Se	3230 1 Asp Ile 3245 r Ser Ser 60 1 Pro Tyr g Asn Lys r Ser Ile 331 r Val Pro 3325 r Pro Leu	Mis Val Ser Thr Ser Gln 3280 Arg Asn 3295 Lys Ser O Asn Arg
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322 Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr 3265 Asp Lys Ala Gln Ile Glu Asp Ala 330 Tyr Phe Ser Asp 3315 His His Thr Gly 3330 Arg Val Asp Arg	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270 Pro Gly Th 3285 Leu Asn Gl Cys Gln Va Val Asp Se 33 Val Ala II 3350	3225 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile hr Thr Asn ln Leu Phe 3305 al Ser Thr 3320 er Leu Cys 335 le Tyr Glu	Gln Leu Value Fro Thr Series 32 Thr Asn Let 3275 Tyr Gln Art 3290 Arg Asn Series 33 Glu Phe Let 3355	3230 1 Asp Ile 3245 2 Ser Ser 50 2 Pro Tyr 3 Asn Lys 2 Ser Ile 331 2 Val Pro 3325 2 Pro Leu 40 2 Arg Met	His Val Ser Thr Ser Gln 3280 Arg Asn 3295 Lys Ser O Asn Arg Ala Arg Thr Arg 3360
Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr 3265 Asp Lys Ala Gln Ile Glu Asp Ala 330 Tyr Phe Ser Asp 3315 His His Thr Gly 3330 Arg Val Asp Arg 3345 Asn Gly Thr Gln Val Asp Gly Tyr 338	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270 Pro Gly Th 3285 Leu Asn Gl Cys Gln Va Val Asp Se 33 Val Ala II 3350 Leu Gln As 3365 Xaa Pro As	3229 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile hr Thr Asn ln Leu Phe 3309 al Ser Thr 3320 er Leu Cys 335 le Tyr Glu sn Phe Thr sn Arg Asn 3389	Gln Leu Value Fro Thr Series 32 Thr Asn Let 3275 Tyr Gln Art 3290 Arg Asn Series 33 Glu Phe Let 3355 Leu Asp Art 3370 Glu Pro Let 5	3230 1 Asp Ile 3245 2 Ser Ser 50 2 Pro Tyr 3 Asn Lys 2 Ser Ile 331 2 Val Pro 3325 2 Pro Leu 40 2 Arg Met 3 Ser Ser 2 Thr Gly 339	Mis Val Ser Thr Ser Gln 3280 Arg Asn 3295 Lys Ser O Asn Arg Ala Arg Thr Arg 3360 Val Leu 3375 Asn Ser O
Ser Phe His Trp 3235 Thr Glu Met Glu 3250 Gln His Phe Tyr 3265 Asp Lys Ala Gln Ile Glu Asp Ala 330 Tyr Phe Ser Asp 3315 His His Thr Gly 3330 Arg Val Asp Arg 3345 Asn Gly Thr Gln Val Asp Gly Tyr	Leu Gly Se Ser Ser Va 32 Xaa Asn Ph 3270 Pro Gly Th 3285 Leu Asn Gl Cys Gln Va Val Asp Se 33 Val Ala II 3350 Leu Gln As 3365 Xaa Pro As	3229 er Thr Tyr 3240 al Tyr Gln 255 he Thr Ile hr Thr Asn ln Leu Phe 3309 al Ser Thr 3320 er Leu Cys 335 le Tyr Glu sn Phe Thr sn Arg Asn 3389	Gln Leu Value Fro Thr Series 32 Thr Asn Let 3275 Tyr Gln Art 3290 Arg Asn Series 33 Glu Phe Let 3355 Leu Asp Art 3370 Glu Pro Let 5	3230 1 Asp Ile 3245 2 Ser Ser 50 2 Pro Tyr 3 Asn Lys 2 Ser Ile 331 2 Val Pro 3325 2 Pro Leu 40 2 Arg Met 3 Ser Ser 2 Thr Gly 339	Mis Val Ser Thr Ser Gln 3280 Arg Asn 3295 Lys Ser O Asn Arg Ala Arg Thr Arg 3360 Val Leu 3375 Asn Ser O

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Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr 3425 3430 3435 3440

Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 3445 3450

<210> 596

<211> 156

<212> PRT

<213> Homo sapiens

<400> 596

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5 10 15

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser 20 25 30

Pro Thr Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155